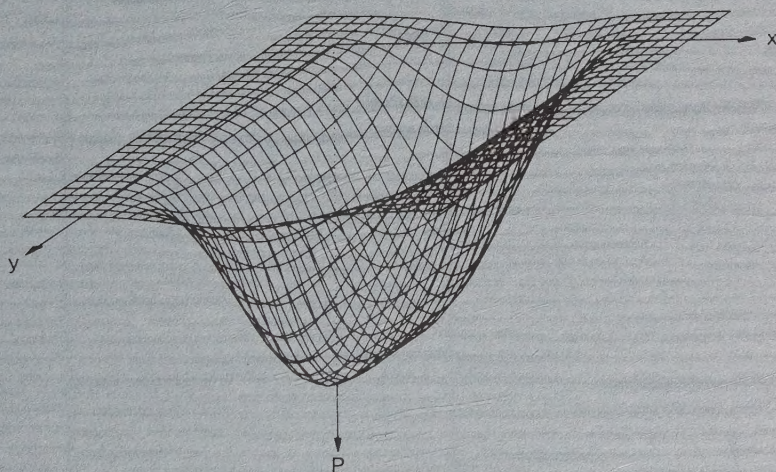


PHYSICS AND TECHNIQUE OF MICROWAVE-INDUCED HYPERTHERMIA IN THE TREATMENT OF MALIGNANT TUMOURS

Per Nilsson



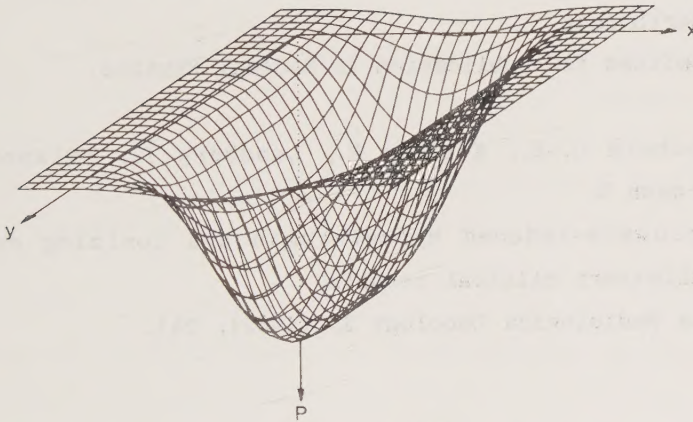
Lund 1984





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This thesis is based on the following papers, which in the text will be referred to by their Roman numerals:

- I Nilsson P., Persson B., Kjellén E., Lindholm C.-E. and Landberg T.

Technique for microwave-induced hyperthermia in superficial human tumours.

Acta Radiologica Oncology 21 (1982), 235.

- II Nilsson P. and Persson B.

Computer-controlled microwave system for clinical hyperthermia.

Submitted for publication in Phys. Med. Biol.

- III Nilsson P.

Absorbed power distributions from single or multiple electromagnetic direct-contact waveguide applicators for hyperthermia.

Submitted for publication in Medical Physics.

- IV Lindholm C.-E., Kjellén E., Landberg T., Nilsson P. and Persson B.

Microwave-induced hyperthermia and ionizing radiation. Preliminary clinical results.

Acta Radiologica Oncology 21 (1982), 241.

Preliminary reports from papers I, II, and IV were given at:

Third International Symposium: Cancer Therapy by Hyperthermia, Drugs, and Radiation. Fort Collins, Colorado, U.S.A., 1980.

First Annual Meeting of the North American Hyperthermia Group (NAHG). Detroit, Michigan, U.S.A., 1981.

Läkarsällskapets riksstämma. Stockholm, 1981 and 1982.

Fifth Meeting of the European Co-operative Hyperthermia Group. Essen, Fed. Rep. Germany, 1983.

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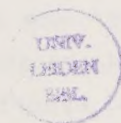
1. PURPOSE OF THE PRESENT WORK

Local tumour control is still a great problem in tumour therapy. About one-fourth of all patients who die from their cancer do so due to locally progressive tumour growth (Suit 1982). There are several explanations for this fact. Local failures in radiation therapy may be due to the existence of anoxic, slowly proliferating radioresistant cells in the tumour. These can not be destroyed by simply raising the absorbed dose; this would result in an unacceptable increase of damage to adjacent normal tissues.

To overcome these problems, different approaches are under investigation throughout the world - one being hyperthermia. Other modalities being studied are radiation treatment with high LET-particles (neutrons, π^- -mesons, heavy ions), conventional radiation treatment in combination with chemotherapy and in combination with oxygen-mimetic substances ("radiosensitizers").

Hyperthermia seems to be a promising treatment modality for malignant tumours, and a more readily available method than the very costly equipment for high LET-particle treatments. There is today, furthermore, a well established biological rationale for hyperthermia, especially in combination with ionizing radiation.

Microwave-induced hyperthermia has previously been used at our department for studying physiological parameters in experimental animal models (Hugander 1983). The aim of the present work has been to develop and evaluate a clinical microwave-system for dependable external induction of hyperthermia in superficial tumours in patients.



2. HISTORICAL BACKGROUND

The use of heat in treating different diseases dates far back in history, as reviewed by Licht (1982). The oldest written document is the Edwin Smith Papyrus from about 3000 B.C., which actually describes the treatment of a tumour by cautery with a "fire drill" (Breasted 1930).

The first author known to report on moderate hyperthermia in more modern times was probably Busch (1866), who described the disappearance of a facial sarcoma after a febrile period caused by erysipelas. A similar case of a patient with a recurrent malignant melanoma was described by Bruns (1888), who reported complete regression of the tumour after a period of high fever. Coley (1893) deliberately induced fever in patients with inoperable tumours by inoculating *S. erysipelatis*, and reported a disease-free survival from one to seven years in 7 of 17 unresectable sarcomas, and a permanent cure in 3 of 17 other inoperable carcinomas. He also developed a bacterial toxin, which was injected in the patients to produce high fever for the treatment of malignant tumours (Coley 1896). In order to be effective, a fever of 39 °C to 40 °C had to be maintained for several days. It is, however, difficult to evaluate the specific role of heat and the direct effect of the bacterial toxin in these cases.

One of the pioneers in using externally induced local hyperthermia was the Swedish gynaecologist, F. Westermarck (1898), who applied hyperthermia on advanced carcinomas of the cervix. The heat was induced by placing a metal coil, through which hot water was circulated, in direct contact with the tumour. The water was heated in a large cistern by a gas flame. The temperature of the water was automatically controlled by a mechanism which regulated the strength of the flame, thus being one of the first clinical hyperthermia systems with automatic

temperature control. The temperature of the metallic loop was 42 - 44 °C, and the treatments usually lasted 48 hours. Good palliative effects were reported, although subsequent healing was rare.

In experimental models, hyperthermia was later seen to have a selective effect on tumour cells (Lambert 1912, N. Westermarck 1927, K. Overgaard 1934).

Hyperthermia as a possible radiosensitizing agent was suggested by Schmidt as early as in 1909, and this was further explored by K. Overgaard (1935).

In spite of the encouraging results described, there were few reports on hyperthermia as an anti-neoplastic agent in tumour therapy during the 1930's and 1940's due to, among other things, inadequate techniques for inducing controlled hyperthermia, and lack of knowledge of the biological mechanisms involved.

More recently, Selawry et al. (1958) reviewed a number of authors who used ionizing radiation and hyperthermia in combination, and concluded that the addition of heat to radiation improved the treatment results. In the 1960's thermobiology began to be more systematically investigated and there was renewed interest in hyperthermia as an adjunct to tumour therapy (Cavaliere et al. 1967).

During the last fifteen years, the increased biological knowledge of the effects of hyperthermia per se, and its combination with other treatment modalities, such as ionizing radiation and drugs, together with the improvement of heat-induction methods, have led to an increased interest in hyperthermia. This is shown in the proceedings of the three international conferences on hyperthermia which have thus far been held (Robinson and Wizenberg 1976, Streffer et al. 1978, Dethlefsen and Dewey 1982).

3. BIOLOGICAL ASPECTS

Several detailed reviews and books have been written on hyperthermia alone, or its combination with other modalities, e.g. Dewey et al. (1977), Field and Bleehen (1979), Hahn (1982), Law (1982), Leith et al. (1977), Oleson and Dewhirst (1983), Overgaard (1977) and Storm (1983). Only the major biological factors involved will be noted here.

3.1. Hyperthermia alone

Hyperthermia (defined as temperatures in the interval of about 41 °C - 45 °C) is cytotoxic per se. In vitro cell-survival curves, depicting the surviving fraction of a cell culture as a function of heating time at elevated temperatures, have shapes similar to the cell-survival curves for ionizing radiation, with or without an initial shoulder followed by an exponential decrease (Fig. 1).

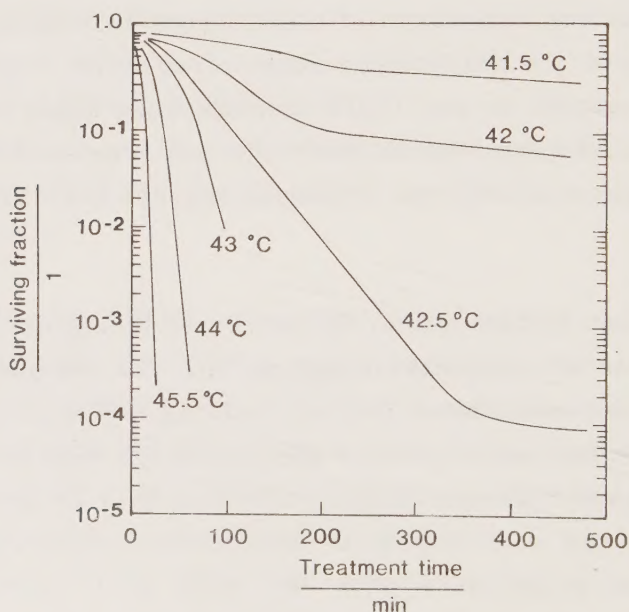


Fig. 1. Survival curves for CHO-cells at different temperatures. (Redrawn from Dewey et al., 1977).

The rate of cell death is strongly dependent on the temperature. This can be illustrated by a so-called "Arrhenius plot" (Fig. 2).

The surviving fraction, S , at the exponential region of the cell-survival curve is represented by:

$$S = \exp(-t/t_0) = \exp(-kt) \quad (1)$$

where $k=1/t_0$ is the slope of the exponential portion of the heat inactivation survival curve, i.e. the heat sensitivity of the cells. The parameter k can also be regarded as the time-rate at which cells are killed. In general, a chemical or biochemical reaction is dependent on temperature. This dependence of the rate-constant, k , can be represented by an empirical equation proposed by Arrhenius:

$$k = A \exp(-E_a/RT) \quad (2)$$

where A is a constant, E_a is the "activation energy", R is the universal gas constant and T is the absolute temperature. The logarithm of the Arrhenius expression gives:

$$\ln k = \ln A - E_a/RT \quad (3)$$

For a constant activation energy E_a , the logarithm of the sensitivity is thus a linear function of the reciprocal of the absolute temperature, where the slope of the curve is related to the activation energy, E_a .

The Arrhenius plot in Figure 2, with data taken from Figure 1, results in two straight lines with a breaking point at about 43 °C, and the activation energies thus differ below and above this point. This bi-phasic Arrhenius curve is commonly, but not always, found. Dewey et al. (1977) suggested that the breaking point reflected different targets for cell-killing. The breaking point between 42 °C and 43 °C has also been observed in in vivo

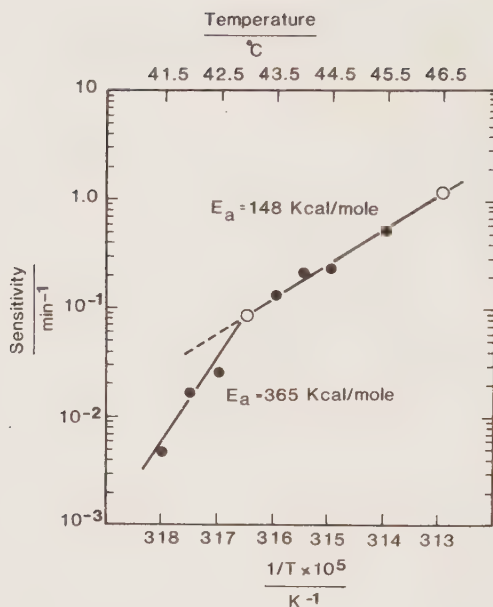


Fig. 2. Arrhenius plot for heat-inactivation of CHO cells (Redrawn from Dewey et al., 1977).

animal studies (Overgaard 1978).

A rule often used to relate time and temperature to the hyperthermic effect is: a one-degree increase in temperature is equivalent to a two-fold decrease in time for the same hyperthermic effect for temperatures above 43 °C, and a four-fold decrease in time for an iso-effect below 43 °C.

The basic mechanisms of cell-killing by heat have not yet been established. Different targets for killing by heat have been described. The permeability, composition or fluidity of the cellular membrane is affected by heat (Wallach 1978). Overgaard (1977) proposed that an increase and damage in lysosomes of the cellular cytoplasm may be a mechanism involved. Heat also affects the cell-nucleus activities; DNA-, RNA- and protein synthesis (Streffer 1982).

The sensitivity of cells to heat varies strongly with different cell lines (Raaphorst et al. 1979). The activation energy,

however, calculated from the Arrhenius relationship, falls in a rather narrow range between about 100 and 200 kcal/mole at temperatures above 43 °C for most cell lines (Henle and Dethlefsen 1980).

Some reports have indicated that malignant cells are more intrinsically sensitive to heat than their normal counterparts (Giovannella et al. 1976), but the opposite has also been reported (Harisiadis et al. 1975).

There are, however, a number of environmental factors affecting the sensitivity of cells to heat. Hypoxic cells, which offer a problem in radiation therapy, are at least as sensitive to heat as are well-oxygenated cells (Gerweck et al. 1974, Kim et al. 1975a). Poorly vascularized parts of tumours may be characterized by nutritional depletion and higher acidity than in the surrounding normal tissue. Both an extracellular reduced pH-value and poor nutrition have been found to enhance cell-killing in vitro (Gerweck 1977, Gerweck et al. 1983, Overgaard 1976, Hahn 1974, Overgaard and Bichel 1977). Besides, hyperthermia preferentially destroys tumour microcirculation, resulting in a further reduction of tumour pH (Bicher et al. 1980). Due to its sluggish blood flow, the tumour may also attain a higher temperature than the surrounding normal tissue for the same amount of absorbed power induced by an external heat source.

Thermotolerance

Hyperthermia can induce transient resistance to further heat treatment in two different ways. One type of thermotolerance is observed with prolonged heating at temperatures below about 43 °C (Dewey et al. 1977, Harisiadis et al. 1977). This type of thermotolerance development is seen after three-to-four hours of heating (see Fig. 1) and may therefore be of limited clinical interest. Sapareto et al. (1978a) have proposed the hypothesis

that the increased activation energy below 43 °C reflects the development of thermotolerance.

The other type of thermotolerance develops after a short exposure to increased temperatures if the cells are then returned to normal temperatures (Gerner and Schneider 1975, Gerner et al. 1976, Henle and Leeper 1976). The molecular mechanism of heat-induced thermotolerance is not known. Thermotolerance in vitro can be seen as a reduction in the slope of the cell-survival curve with or without a change in the shoulder of the curve. This phenomenon has also been found in vivo both for normal tissue and solid tumours (Henle and Dethlefsen 1978, Nielsen 1984). The degree of thermotolerance and its kinetics are dependent on the initial heat dose (Nielsen 1984), and a larger amount of heat resistance is seen with increasing pre-heat dose. Thermotolerance is, however, partly inhibited by poor nutritional conditions and an acidic environment (Gerweck 1977, Nielsen 1984), factors that may be present in a solid tumour. Thermotolerance usually develops to its maximum within 24 hours, decays slowly and has usually disappeared after 2-4 days, though it has been seen to persist for up to 7 days in a human melanoma xenograft (Rofstad and Brustad 1984). Since the clinical use of hyperthermia depends on fractionated treatments, this type of thermotolerance must be considered when clinical treatment schedules are planned.

3.2. Hyperthermia in combination with ionizing radiation

The combination of hyperthermia and ionizing radiation offers many potential advantages. Hyperthermia radiosensitizes cells, resulting in a synergistic effect when the two modalities are combined (Sapareto et al. 1978b). The direct hyperthermic radiosensitization leads to a reduction of D_0 (the inverse of the slope of the exponential region of the cell-survival curve for ionizing radiation), and a reduced repair of sublethal damage as evidenced by a reduction of the shoulder (the quasithreshold

dose, D_q) of the survival curve (Ben-Hur et al. 1974). Hyperthermia may also reduce the repair of potentially lethal x-ray damage (Li et al. 1976), which mainly occurs in cells with poor nutrition. Furthermore, it has been shown that the relatively radioresistant cells in the S-phase of the cell cycle, are the cells most sensitive to heat (Westra and Dewey 1971). Heat may also be more efficient in hypoxic cells than in well-oxygenated cells, leading to a decreased oxygen-enhancement ratio, OER (Kim et al. 1975b). Myers and Field (1979) did not, however, find any reduction in OER by hyperthermia in their experimental animal system.

The combined effect of heat and radiation is described by the thermal enhancement ratio, TER, defined as:

$$TER = D_x / D_{x+ht} \quad (4)$$

where D_x is the absorbed radiation dose to produce a given level of biological damage for radiation alone, and D_{x+ht} is the absorbed radiation dose to obtain the same damage when radiation and hyperthermia are combined.

TER-values for different tissues have been given by various authors, e.g. Hill and Denekamp (1979), Hume and Field (1978), Law et al. (1977) and Stewart and Denekamp (1978). For the combined treatment to be beneficial, the TER-value should be higher for tumour tissue than for its surrounding normal tissue, if the same radiation and hyperthermia doses are given to the two tissue types. The therapeutic gain factor, TGF, is defined as:

$$TGF = TER_t / TER_n \quad (5)$$

where TER_t and TER_n are the thermal enhancement ratios for tumour and normal tissues, respectively, and should thus be greater than 1.

The maximal TER-values are obtained when heat and radiation are combined simultaneously, but in this case there does not seem to be any significant difference in thermal enhancement between tumour and normal tissue, as shown in different experimental animal systems. When the two treatment modalities are separated, however, the thermal enhancement ratios are decreased, but not to the same extent in tumour and normal tissue. If the spacing is more than three-to-four hours between radiation and hyperthermia, thermal enhancement is lost in normal tissue, but persists to some extent up to 24 hours in the tumour, resulting in a TGF greater than 1 (Hill and Denekamp 1979, Stewart and Denekamp 1978, Overgaard 1980). If the tumour and the surrounding normal tissue are heated equally, an optimal effect should, according to these results, be obtained, if radiation preceded hyperthermia treatment by a four-hour interval, thus not using the hyperthermic radiosensitization, but the cytotoxicity of hyperthermia on radioresistant tumour cells. If a selective tumour heating is possible, on the other hand, the most beneficial regimen would be simultaneous hyperthermia and radiation treatment. The problems associated with fractionation and sequencing of heat and radiation, and the importance of thermotolerance for clinical treatment, have been discussed by Overgaard (1982) and Overgaard and Nielsen (1984).

4. PHYSICAL ASPECTS

4.1. Hyperthermia-induction methods

The physical methods employed for power deposition in local and regional clinical hyperthermia are:

- Ultrasound at frequencies of about 0.3 - 3 MHz,
- Electromagnetic fields at radiofrequencies < 300 MHz and
- Electromagnetic radiation at microwave frequencies 300-2450 MHz.

Several reviews and books on physics and techniques of electromagnetic and ultrasonic hyperthermia have been published, e.g. Atkinson (1979), Cristensen and Durney (1981), Hand and ter Haar (1981), Hunt (1982) and Nussbaum (1982). The different heat-induction methods will therefore only be briefly discussed in this section.

Ultrasound

Tissue heating with ultrasound may be carried out with external transducers, appropriately coupled to the surface of the body. Ultrasound is significantly more penetrating in fat than in muscle tissue. For example at 1 MHz, the penetration depths are 4.4 cm in muscle and 31.3 cm in fat. The short wavelength in tissue, less than a few mm, makes it possible to focus ultrasonic energy in small volumes at large depths. Due to the large impedance mismatch between soft tissue and air, and between soft tissue and bone, however, these interfaces cause almost complete reflection of the ultrasonic energy. The anatomical locations where ultrasound can be applied are thus limited.

Electromagnetic fields

Capacitive radiofrequency techniques

A technique often used in diathermy at the ISM-frequencies (Industrial, Scientific and Medical frequencies) 13.56 MHz and 27.12 MHz, is the application of a pair of capacitor plates excited by the radiofrequency generator. The tissue is heated due to displacement currents produced by the electric field in the tissue between the plates. Theoretically, the technique has a potential for deep-heating in a homogeneous medium. The boundary conditions at a fat/muscle layer approximately parallel to the plates will, however, result in a preferential heating of the fatty tissue (Guy et al. 1974). To obtain a uniform field distribution, the plates should be large compared to the distance between them. The capacitive technique has been used in clinical hyperthermia by Brezovich et al. (1981). To overcome the problems with excessive heating of subcutaneous fat layers, Sugaar and Leveen (1979) used multiple pairs of plates arranged in a "cross-fire" configuration.

Inductive radiofrequency techniques

When an oscillating magnetic field is applied to a biological medium, eddy currents are generated, which produce heating in the tissue. The most conventional type of applicator is the so-called "pancake" coil (Guy et al. 1974) often used in diathermy at 13.56 MHz or 27.12 MHz. This applicator is suitable for heating rather superficial tissue volumes. Different coil designs have been discussed by Lerch and Kohn (1983). Storm et al. (1981) described a hyperthermia system (commercially available under the tradename "Magnetrotde"), consisting of an annular one-turn coil excited at 13.56 MHz for regional deep-heating. The ability of this coil configuration to produce deep-heating has been debated in the

literature by e.g. Oleson (1982) and by Paliwal et al. (1982). A new type of inductive applicator working at about 150 MHz has recently been described by Bach Andersen et al. (1984). It has been used clinically for hyperthermia treatment of superficial tumours.

Radiative electromagnetic techniques

Techniques based on radiative electromagnetic apertures have mostly been used at the microwave ISM-frequencies of 2450 MHz, 915 MHz and 434 MHz. Radiative apertures working at lower frequencies have, however, also been used for regional deep heating. Turner (1982) described a technique with multiple phased applicators in a circular configuration (the Annular Phased Array, BSD Medical Corporation, USA). Recently, Lagendijk (1983) presented a coaxial TEM RF/microwave applicator for deep-body hyperthermia.

This work only considers local hyperthermia externally induced by direct-contact waveguide applicators excited at microwave frequencies.

4.2. Basic physics of interaction between microwaves and biological matter

Microwaves are defined as the region of the electromagnetic spectrum with frequencies ranging from 300 MHz ($\lambda_0=1$ m) to 300 GHz ($\lambda_0=1$ mm). The discussion below is also valid for electromagnetic waves with lower frequencies (the radiofrequency range). There are three basic mechanisms involved in the biophysical interaction processes:

1. Displacement or drift of free charges (electrons, ions) due to the electric field.
2. Polarization of atoms and molecules.
3. Orientational polarization of permanently existing dipoles (i.e. water, lipids).

Through the oscillations of free charges (conduction losses) and the relaxation of electric dipoles (dielectric losses), energy is removed from the electromagnetic field and converted to kinetic energy of the tissue molecules, resulting in a temperature rise in the tissue (Johnson and Guy 1972).

The macroscopic interaction between the electromagnetic field and the tissue is governed by the dielectric permittivity, $\epsilon = \epsilon'_r \epsilon_0$, the magnetic permeability, $\mu = \mu'_r \mu_0$, and the conductivity, σ , through Maxwell's equations, which on differential form in biological tissue are given by:

$$\vec{\nabla} \times \vec{E} = - \mu \frac{\delta \vec{H}}{\delta t} \quad (6)$$

$$\vec{\nabla} \times \vec{H} = \sigma \vec{E} + \epsilon \frac{\delta \vec{E}}{\delta t} \quad (7)$$

$$\vec{\nabla} \cdot \vec{E} = 0 \quad (8)$$

$$\vec{\nabla} \cdot \vec{H} = 0 \quad (9)$$

where:

$\vec{E}$ = electric field vector

$\vec{H}$ = magnetic field vector

t = time

ϵ'_r = relative permittivity (dielectric constant)

$\epsilon_0 = 8.854 \cdot 10^{-12} \text{ AsV}^{-1}\text{m}^{-1}$ = permittivity of free space

μ'_r = relative permeability ($\mu'_r = 1$ for tissue)

$\mu_0 = 4\pi \cdot 10^{-7} \text{ VsA}^{-1}\text{m}^{-1}$ = permeability of free space

The time derivative of Equation 7 gives:

$$\vec{\nabla} \times \frac{\delta \vec{H}}{\delta t} = \sigma \frac{\delta \vec{E}}{\delta t} + \epsilon \frac{\delta^2 \vec{E}}{\delta t^2} \quad (10)$$

Equations 6 and 10 result in:

$$\vec{\nabla} \times \vec{\nabla} \times \vec{E} = -\mu\sigma \frac{\delta \vec{E}}{\delta t} - \mu\epsilon \frac{\delta^2 \vec{E}}{\delta t^2} \quad (11)$$

The vector identity:

$$\vec{\nabla} \times \vec{\nabla} \times \vec{E} = \vec{\nabla} (\vec{\nabla} \cdot \vec{E}) - \vec{\nabla}^2 \vec{E} \quad (12)$$

and Equations 8 and 11 result in the vector wave equation:

$$\vec{\nabla}^2 \vec{E} - \mu\sigma \frac{\delta \vec{E}}{\delta t} - \mu\epsilon \frac{\delta^2 \vec{E}}{\delta t^2} = 0 \quad (13)$$

and the corresponding expression is valid for H.

We will only consider time harmonic radiation fields of the type $\vec{E} e^{-j\omega t}$, where ω is the angular frequency of the electromagnetic field. Replacing $\vec{E}$ in Equation 13 with the time harmonic form gives:

$$\vec{\nabla}^2 \vec{E} + j\mu\sigma\omega \vec{E} - \mu\epsilon\omega^2 \vec{E} = 0 \quad (14)$$

The wave equation can thus be written as:

$$\vec{\nabla}^2 \vec{E} + \gamma^2 \vec{E} = 0 \quad (15)$$

where γ is the complex propagation constant:

$$\gamma^2 = j\mu\sigma\omega - \mu\epsilon\omega^2 \quad (16)$$

Furthermore:

$$\begin{aligned} \gamma &= \alpha + j\beta = \\ &= \{j\omega\mu(j\omega\epsilon_o\epsilon'_r + \sigma)\}^{\frac{1}{2}} = j\omega \{ \mu\epsilon_o(\epsilon'_r - j\frac{\sigma}{\omega\epsilon_o}) \}^{\frac{1}{2}} \end{aligned} \quad (17)$$

where the quantity:

$$\epsilon_o(\epsilon'_r - j\frac{\sigma}{\omega\epsilon_o}) = \epsilon_o(\epsilon'_r - j\epsilon''_r) = \epsilon^* \quad (18)$$

is defined as the complex permittivity. The real part of ϵ^* describes the dielectric properties of the medium, and the imaginary part accounts for the losses in the medium.

Energy absorption in the medium is often represented by the dissipation factor or loss tangent, $\tan\delta$, defined as:

$$\tan\delta = \epsilon''_r/\epsilon'_r \quad (19)$$

The loss tangent describes the ratio of lossy components to lossless components. A "perfect" dielectric material has no losses, $\tan\delta=0$ (as $\sigma=0$), and there is no attenuation of the wave.

The parameters α and β are obtained by combining Equations 16 and 17:

$$\alpha = \omega \left(-\frac{\mu\epsilon_o\epsilon'_r}{2} \right)^{\frac{1}{2}} \left(\left\{ 1 + \left(\frac{\sigma}{\omega\epsilon_o\epsilon'_r} \right)^2 \right\}^{\frac{1}{2}} - 1 \right)^{\frac{1}{2}} \quad (20)$$

and

$$\beta = \omega \left(\frac{\mu \epsilon_0 \epsilon'_r}{2} \right)^{\frac{1}{2}} \left(\left\{ 1 + \left(\frac{\sigma}{\omega \epsilon_0 \epsilon'_r} \right)^2 \right\}^{\frac{1}{2}} + 1 \right)^{\frac{1}{2}} \quad (21)$$

A particular solution of Equation 16 for a plane wave propagating in the z-direction with amplitudes E_0 and H_0 , respectively, is:

$$\vec{E} = E_0 e^{j\omega t - \gamma z} \hat{x} = E_0 e^{-\alpha z} e^{-j(\omega t + \beta z)} \hat{x} \quad (22)$$

$$\vec{H} = H_0 e^{j\omega t - \gamma z} \hat{y} = H_0 e^{-\alpha z} e^{-j(\omega t + \beta z)} \hat{y} \quad (23)$$

where $\hat{x}$ and $\hat{y}$ are unit vectors. The field strength thus decays exponentially with the attenuation coefficient, α , which is dependent on frequency due to the frequency dependence of ϵ'_r and σ .

The penetration depth or skin depth, d_s , is the distance at which the amplitude has decreased to $1/e$ (37%) of its value at the reference depth:

$$d_s = 1/\alpha \quad (24)$$

The imaginary part of the propagation constant, β , determines the wavelength, λ , in the tissue:

$$\lambda = 2\pi/\beta \quad (25)$$

The dielectric constant, ϵ'_r , and the conductivity, σ , of biological tissue have been measured by several authors both in vitro and in vivo, and are summarized by Stuchly and Stuchly (1980). More recent data have been reported by Gabriel et al. (1983), Kraszewski et al. (1982), Stoy et al. (1982) and Stuchly et al. (1981, 1982a, 1982b).

Different tissues can roughly be divided into two groups regarding dielectric properties:

1. High water content: e.g. muscle, skin, internal organs, and
2. Low water content: e.g. fat, bone.

The parameters ϵ'_r and σ have been plotted in Figure 3 as a function of frequency from published data on tissues with high and low water contents, respectively (Johnson and Guy 1972).

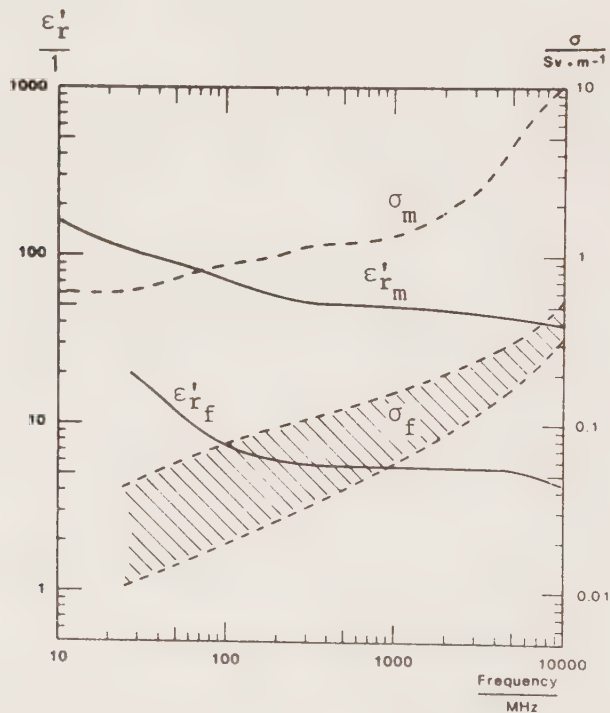


Fig. 3. Dielectric constant (ϵ'_r) and conductivity (σ) as a function of frequency for muscle-like (m) and fatty (f) tissues.

In Figures 4 and 5 the penetration depth, d_s , and the wavelength, λ , have been plotted as functions of frequency for the two types of tissues. Penetration is always much larger in fatty tissue than in muscle tissue, and the penetration depth increases with

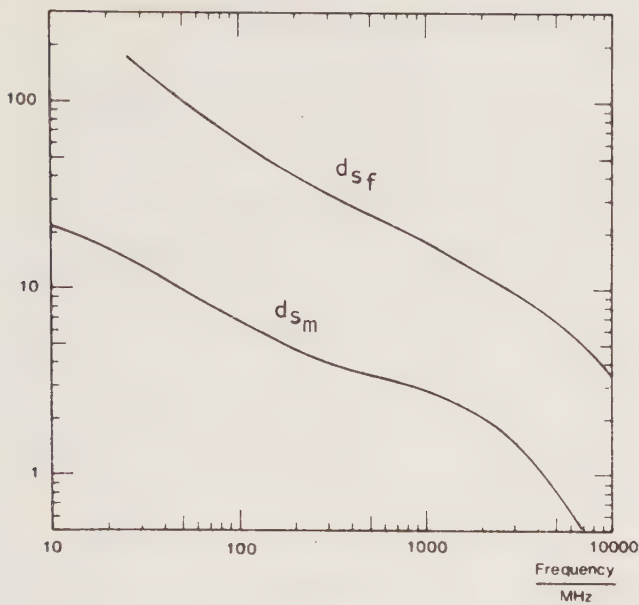


Fig. 4. Penetration depth (d_s) as a function of frequency for muscle-like (m) and fatty (f) tissues.

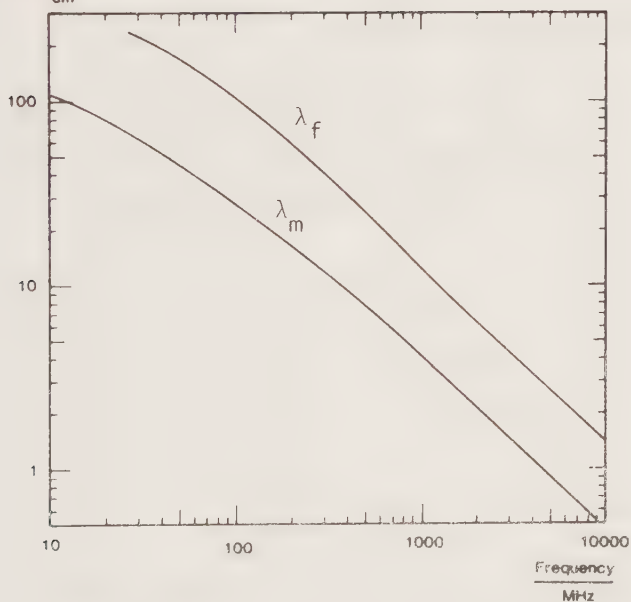


Fig. 5. Wavelength (λ) as a function of frequency for muscle-like (m) and fatty (f) tissues.

decreasing frequency.

It must be kept in mind that the penetration depth discussed above is strictly valid only for a **plane wave** impinging on a semi-infinite homogeneous medium. In clinical hyperthermia, the complicated near fields of the radiating aperture must be considered (see Paper III). In addition, the electromagnetic wave is refracted, diffracted and dispersed when encountering inhomogeneities in the medium, e.g. muscle-fat interfaces. For specific thicknesses of the materials, standing wave patterns can be obtained, creating hot spots in the irradiated tissue (Johnson and Guy 1972).

If the electric field is known in a specific point in the tissue, the absorbed power can be calculated. The time-rate at which energy traverses a surface in an electromagnetic field is given by the Poynting vector, $\vec{S}$:

$$\vec{S} = \vec{E} \times \vec{H} \quad (\text{W m}^{-2}) \quad (26)$$

a quantity often used in radiation protection.

The amount of power absorbed by the tissue can be derived from the Poynting vector and Maxwell's equations, resulting in the power absorbed per unit volume of tissue (the power density), P :

$$P = \frac{1}{2} \sigma |\vec{E}|^2 \quad (\text{W m}^{-3}) \quad (27)$$

In dosimetric applications, the SAR-concept (Specific Absorption Rate) is often used, and is defined as:

$$\text{SAR} = \frac{d}{dt} \left(\frac{dW}{dm} \right) \quad (\text{W kg}^{-1}) \quad (28)$$

where dW is the increment in absorbed energy in the mass-element dm during the time-interval dt (NCRP 1981). Hence:

$$\text{SAR} = \frac{\sigma}{2\rho} |\vec{E}|^2 \quad (\text{W kg}^{-1}) \quad (29)$$

where ρ is the density of the tissue.

Drawing parallels to ionizing radiation, the quantity S is related to the quantity "energy fluence rate" and SAR corresponds to the "absorbed dose rate".

4.3. Heat transfer in tissue

The temperature distribution in tissue heated by an external source is, in addition to the absorbed power distribution from the source, governed by heat transfer due to conduction and blood flow.

Thermal conduction during steady state conditions follows Fourier's law, i.e. the heat flux by conduction is proportional to the temperature gradient, where the constant of proportionality is the thermal conductivity, k . The rate of energy flow per unit area (in one dimension) is thus:

$$\frac{Q}{A} = -k \frac{\delta T}{\delta x} \quad (\text{W m}^{-2}) \quad (30)$$

Transient heat conduction is described by another equation of Fourier:

$$\nabla^2 T = \frac{1}{\alpha} \frac{\delta T}{\delta t} \quad (31)$$

where

$$\alpha = \frac{k}{\rho_t c_t} \quad (32)$$

is the thermal diffusivity of the medium, ρ_t is the density and c_t is the tissue heat capacity. The parameter α defines the ability of a thermally perturbed system to relax back to its

steady state condition.

A tabulation of the thermal properties of tissues has been given by Bowman et al. (1975).

The equation describing the conservation of thermal energy in living tissue heated with an external source, the "bio-heat transfer equation", is then in differential form, :

$$\rho_t c_t \frac{\delta T}{\delta t} = \nabla(k \nabla T) + q_b + q_m + q_a \quad (33)$$

where

ρ_t = tissue density (kg m^{-3})

c_t = tissue heat capacity ($\text{J kg}^{-1} \text{K}^{-1}$)

T = tissue temperature (K)

k = tissue thermal conductivity ($\text{W m}^{-1} \text{K}^{-1}$)

q_b = rate of heat exchange with blood flow (W m^{-3})

q_m = rate of metabolic heat generation (W m^{-3})

q_a = rate of energy absorbed by the tissue from an external source (W m^{-3})

The rate of change of stored thermal energy, given by the left-hand term of the bio-heat equation, is thus dependent on tissue thermal conduction, thermal convection via the blood flow, metabolic heat-generation and the rate of energy absorbed by the tissue from an external heat-source.

The major factor determining the temperature distribution in heated tissue is the blood flow (Bowman 1981). The blood flow term in the bio-heat equation is given by an expression describing the difference between the thermal energy brought into the actual volume-element by the arterial blood and the thermal energy carried away with the venous blood. This was originally proposed by Pennes (1948), who assumed that the capillary blood bed was the site of the major heat-exchange between tissue and blood, and that the venous blood leaves the tissue at tissue

temperature. The rate of heat-exchange with the blood flow can then be expressed as:

$$q_b = w c_b \rho_b (T_a - T_v) = w c_b \rho_b (T_a - T) \quad (34)$$

where

- w = blood perfusion rate (s^{-1})
- c_b = blood heat capacity ($J \text{ kg}^{-1} \text{ K}^{-1}$)
- ρ_b = blood density (kg m^{-3})
- T_a = arterial blood temperature (K)
- T_v = venous blood temperature (K)

Analytical or numerical calculations, based on the bio-heat transfer equation, in simple tissue models and for different heat sources have been made by e.g. Bowman (1981), Brezowich et al. (1983), Foster et al. (1978), Hand et al. (1982), Lagendijk (1982a), Ozimek and Cetas (1982) and Strohhenn (1982, 1983).

There are, however, a number of limitations associated with the bio-heat transfer equation. It does not take into account the real temperature of the blood entering an arbitrary mass-element of the tissue, as the blood flow term according to Equation 34 assumes that the blood enters all tissue elements at the body core temperature (arterial blood temperature) and leaves at the actual tissue temperature. The bio-heat transfer equation does not either describe the effect of discrete vessels, which has a large influence on the temperature distribution (Bowman 1980, Chen and Holmes (1980), Lagendijk 1982b). A three-dimensional thermal model, which includes the influence of blood flow in discrete vessels, has been developed by Lagendijk et al. (1984).

5. THE PRESENT HYPERTHERMIA SYSTEM

The equipment and the computer hardware and software of the hyperthermia system are described in Papers I and II.

5.1. Microwave applicators

Microwave applicators can be of either spaced or direct contact type. Most of the commercially available applicators at microwave frequencies are those used for physiotherapy. These are usually spaced antennae having drawbacks such as poor coupling of electromagnetic energy into tissue and large amounts of stray radiation, and are thus not very suitable for hyperthermia. It is, furthermore, not possible to measure the net power absorbed in the patient.

Many types of direct contact applicators have been described in the literature and have been surveyed by Kantor (1981). In the present hyperthermia system, waveguide applicators with circular, square or rectangular apertures have been used (Papers I,II,IV).

The air-filled, circular TE_{11} -applicator (I) for 2450 MHz has the ability to be circularly polarized, which results in a heating pattern that is equal along all of the diameters of the aperture (Kantor et al. 1978). The absorbed power distribution parallel to the aperture at 5 mm depth in a planar muscle-equivalent phantom in direct contact with the applicator is shown in Figure 6, measured after a short (30 seconds) high-power microwave pulse (200 W CW) by a thermographic camera with a split-phantom technique similar to that described by Kantor and Cetas (1977). The half-power width is about 50 mm.

The other applicators are excited in the TE_{10} -mode by a coaxial line probe antenna according to Collin (1960). Applicators

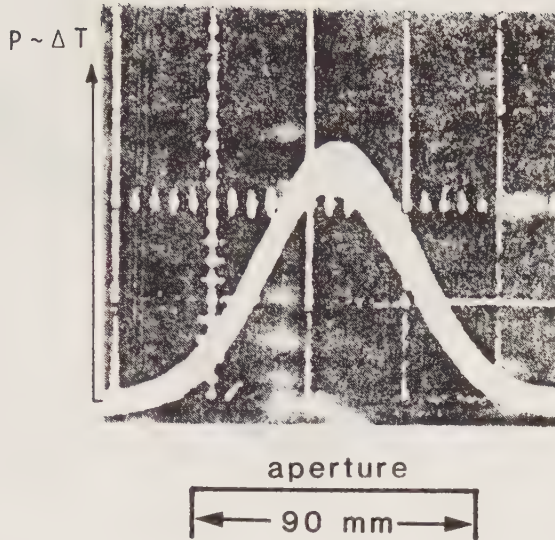


Fig. 6. Absorbed power distribution, P , for the circular TE_{11} -apliator parallel to the aperture at 5 mm depth in a muscle-equivalent phantom.

excited in this way have also been described by Sandhu et al. (1978a) and Cheung et al. (1981).

The applicator-tissue boundary reflects a significant amount of energy, which necessitates a tuning device on the coaxial line between the generator and the applicator in order to minimize the standing-wave-ratio (II). The air-filled applicators are provided with a quarter wavelength transformer at the aperture (I). The transformer, a low-loss dielectric material with $\epsilon'_r \approx 7$, reduces the reflected power-level to less than 10% of the incident power, and the external tuner is not necessary for these applicators.

The major drawback with the TE_{10} -applicator is the variation of the electric field strength in the direction perpendicular to the polarization direction (II,III). The power distribution, P , parallel to the aperture at 10 mm depth in a muscle-equivalent medium from a $10 \times 10 \text{ cm}^2$ TE_{10} -applicator at 915 MHz is shown in an isometric plot in Figure 7. The applicator is polarized in the

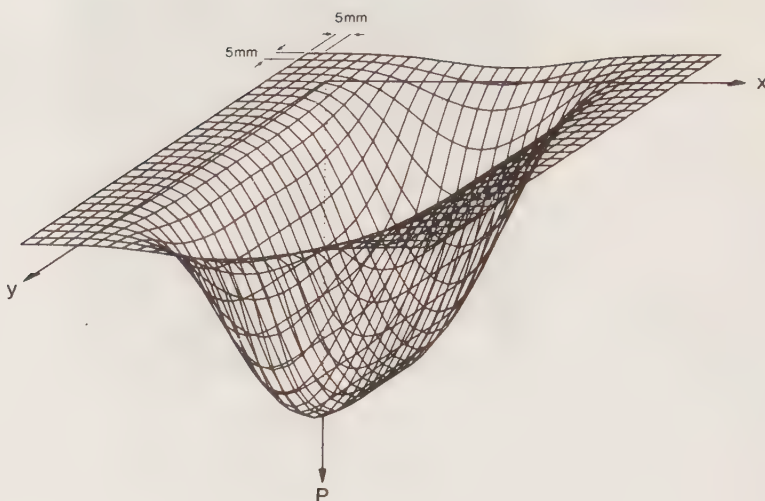


Fig. 7. Absorbed power distribution, P , parallel to the aperture surface at 10 mm depth for a $10 \times 10 \text{ cm}^2$ TE_{10} -applicator at 915 MHz.

y-direction and the absorbed power distribution is calculated according to the method described in Paper III.

To obtain a more homogeneous E-field distribution, rectangular applicators loaded with dielectric slabs have been described. These structures can support a TEM-wave in the central region at a frequency governed by the dielectric constant and the thickness of the slab material (VanKoughnett and Wysloutzil 1972). Slab-loaded applicators for 2450 MHz have been evaluated by Kantor and Witters (1980), and used by e.g. Cheung and Robinson (1977) for hyperthermia experiments with mouse tumours. Sandhu et al. (1978b) described an applicator excited simultaneously in the TE_{10} - and TE_{01} -modes to improve the heating pattern. Single or double ridge waveguides have a rather uniform heating area, but it is small compared to the physical size of the applicator (Hand 1982). Antennae based on microstrip technique have been described

by Bahl et al. (1982) and Sandhu and Kolozsvary (1983). These devices have intense near fields and a narrow resonant frequency band dependent on the antenna load.

Since the core of solid tumours generally has a lower blood perfusion than the viable periphery (Cravalho et al 1980), the optimal applicator in clinical hyperthermia, would be one with an aperture that preferentially heated the periphery of the tumour. This can be achieved by exciting higher-order modes in the waveguide than the fundamental TE_{10} -mode, e.g. the box horn antenna (Stuchly and Stuchly 1978). Another way is to use multiple applicators, as shown in Paper III.

5.2. Thermometry

As discussed in Chapter 3, the sensitivity of heat inactivation of cells is strongly dependent on temperature. According to in vitro studies, a temperature change of only a few tenths of a degree can considerably affect the results (Dewey et al. 1977).

Christensen (1983) has proposed some factors required by a clinical thermometry system: The thermometric accuracy and resolution within a temperature range from 20 °C to 55 °C should be 0.1 °C. The temporal resolution should be better than one second. A spatial resolution of about one cm is desirable.

The spatial resolution is, of course, impossible to achieve with invasive point thermometry. The requirements put forth for the thermometric accuracy, precision and resolution are met by the clinical thermometry system described in detail in Paper II.

Absolute thermometry is performed with a temperature-regulated waterbath by means of a precision thermistor probe (Thermometrics, USA, Temperature standard S-10-4) traceable to NBS (National Bureau of Standards, Washington, USA) with a

technique similar to that described by Cetas and Connor (1978).

A new temperature-reading unit and multiple sensor thermistor probes (Lund Science AB, Lund) have recently been incorporated in the system. The temperature-reading unit is provided with 16 channels (expandable to 64 channels). The multisensor probes have either two or three thermistor beads and are teflon-coated, with an outer diameter of 0.7 mm.

Temperature measurements in electromagnetic fields

The major drawback with conventional thermistor or thermocouple probes is the interaction between the metallic leads of the probe and the electromagnetic field. The tangential component of the electric field along the wire induces an electric field, E_t , in the wire, which results in a current density:

$$i_t = \sigma E_t \quad (\text{Am}^{-2}) \quad (35)$$

where σ is the conductivity of the metallic lead. This current density causes perturbations in different ways: The wire re-radiates electromagnetic fields (and thus disturbs the field in the surrounding tissue), the temperature probe is heated by the current with the power density:

$$P = i_t^2 / \sigma \quad (\text{Wm}^{-3}) \quad (36)$$

and the current causes electromagnetic interference resulting in pick-up noise in the electronics of the temperature-reading unit. The magnitude of the perturbation lessens with decreasing diameter of the leads.

The perturbation can be minimized by using leads with a high resistivity. Several "non-perturbing probes" have been described in the literature.

Bowman (1976) used a thermistor sensor with high-resistance plastic leads containing graphite to attain a high resistivity. These types of probes are used in the BSD-1000 hyperthermia system (BSD Medical Corporation, USA). Their major drawback is their large diameter, roughly 1 mm. The probe is used together with a closed-end catheter with an outer diameter of about 2 mm for insertion of the probe into the tissue. The Bowman type of thermistor is commercially available as a single probe unit (VITEK Inc., USA).

Several probes based on non-conducting optical fiber leads with different sensors have been described. Rozzell et al. (1974) used a liquid crystal as a sensor. Cetas (1977) described a birefringent sensor of LiNbO_3 . Wickersheim and Alves (1979) developed a fluorescent-type sensor made of two phosphors. Christensen (1977) used a semiconductor crystal, GaAs, as a temperature sensor. This type of probe is used in the Clini-Therm hyperthermia system (Clini-Therm Corporation, USA).

The liquid crystal probe is commercially available as a single-channel unit (RAMAL, USA). The diameter of the probe is 2 mm and the accuracy is about 0.2 °C. The fluorescent phosphor probe is also available as a single probe unit (LUXTRON 1000B, LUXTRON, USA).

Concerning interaction with electromagnetic fields, these probes are superior to conventional thermistor or thermocouple probes with metallic leads, but none of the temperature probes are really non-perturbing (Hochuli 1981). A perfect temperature probe should have the same dielectrical properties as tissue.

Single-channel units are not suitable in a clinical hyperthermia system. Some multichannel systems with non-perturbing probes have recently become commercially available for medical use: Thermosentry 1200 (GaAs-sensors) from Clini-Therm Corporation,

Model 2000 Multichannel Fluoroptic Thermometer (fluorescent phosphor sensor) from LUXTRON and BSD-200 (thermistor sensor with high-resistance leads) from BSD Medical Corporation. All of these units are, however, very expensive.

When using conventional thermistor or thermocouple probes, the disturbance of the temperature signal by the electromagnetic field must be carefully studied. The interaction between the electromagnetic field and the thermistor probe is described in Paper II. When the probe is placed perpendicularly to the electric field from the applicator, no perturbation can be observed. If the most severe case is considered, with the thermistor leads parallel to the electric field, a marked distortion of the temperature signal is obtained due to noise pick-up and self-heating of the probe. This perturbation has, however, completely disappeared in a static muscle-equivalent phantom three seconds after the microwave power has been shut off. By using a pulsed irradiation technique, the influence of the perturbation can thus be minimized (I, II).

5.3. Surface temperature control

A surface temperature control system is indispensable in clinical microwave hyperthermia since the maximal power absorption is in the very superficial parts of the tissue. By cooling the surface, the maximal temperature rise can be shifted to larger depths (Foster et al. 1978), and the depth at which therapeutic temperatures can be obtained will thus be increased. Surface-cooling has been seen to influence the temperature distribution down to at least one cm of depth. Most tumours accessible with microwave-induced hyperthermia, however, require heating, both subcutaneously and at depth, and extreme surface-cooling has therefore seldom been used.

Two types of surface temperature control are used. For 2450 MHz,

cooling is accomplished by pressing an air stream through the applicator (I). With 915 MHz, surface temperature regulation is performed by circulating temperature controlled de-ionized water through a plastic bag, placed between the applicator and the patient (II). The thickness of the water bolus has usually been 15 - 20 mm.

The water cooling system has proven to be superior to cooling with air. With the water system, it is much easier to keep a constant pre-determined surface temperature level during the whole hyperthermia treatment. The water bolus also acts as a coupling medium between the applicator and the patient, improving the power transfer to the tissue, especially at anatomical locations with a complex surface topography (e.g. in the head-and-neck area). It also decreases microwave leakage. The magnitude of this decrease can be shown by a simple phantom experiment. With a 20 mm thick water bolus between the applicator and the phantom (size: $25 \times 25 \times 7 \text{ cm}^3$), and with a net power to the applicator ($12 \times 12 \text{ cm}^2$) of 150 W CW, the equivalent power density in the aperture plane 5 cm from the applicator wall is 1.3 mW cm^{-2} , as measured with a radiation field monitor (Holaday Model HI 3002, with its isotropic E-field probe). This is below the maximum permissible whole-body exposure value of 3 mW cm^{-2} at 915 MHz, recommended by the American National Standards Institute (ANSI). When the water bolus was replaced with a 20 mm air gap, the exposure value increased to 40 mW cm^{-2} at the same position. The 3 mW cm^{-2} and 1 mW cm^{-2} levels were in this case at distances from the aperture of 20 cm and 30 cm, respectively.

Regarding these items, it would thus be preferable to use a water bolus for skin temperature control also at 2450 MHz. The power absorption in water at this frequency is, however, quite large. Interpolating in the tabulated permittivity data of Von Hippel (1954), the loss tangent for water at 35°C (a typical bolus temperature, see Paper II) is:

$$\tan \delta = 0.105 \text{ Sm}^{-1} \text{ at } 2450 \text{ MHz},$$

$$\tan \delta = 0.038 \text{ Sm}^{-1} \text{ at } 915 \text{ MHz}$$

and with a dielectric constant, ϵ_r' , of 74 for both frequencies.

For a plane wave, this results in a penetration depth of 43 mm for 2450 MHz, and of 320 mm for 915 MHz. With a water thickness of 20 mm (and still considering a plane wave), about 60% of the incident power at 2450 MHz would thus be absorbed in the water bolus, while the corresponding figure for 915 MHz is about 10%.

5.4. Computer software

The first hyperthermia control program was written in BASIC and assembly language (I). The control algorithm, based on varying the length of the microwave pulses (I), was chosen due to difficulties in finding a proper electronic solution of interfacing and controlling the power-level of the Siemens 2450 MHz generator.

New system software was later implemented on the microcomputer, and the hyperthermia control program was up-dated and rewritten in FORTRAN and assembly routines resulting in a more structured and versatile program (II). With the microwave/RF-generator described in Paper II and used at 915 MHz, the control algorithm was considerably improved by using fixed lengths of the microwave pulses, and control of the net power level by varying the duty-frequency of the generator during the pulse. This resulted in smoother time/temperature curves.

During a hyperthermia treatment session it is, however, always possible to disconnect the computer control and regulate the microwave power level manually, thus only using the computer as a data logger.

5.5. Phantom studies

The use of phantoms in thermal dosimetry has been described in detail by Cetas (1983).

Contrary to the case with ionizing radiation, the results from static phantom experiments with non-ionizing electromagnetic radiation can not be directly applied in patient treatments. The thermal distribution in the heated volume is governed by the absorbed power distribution from the electromagnetic source, and by heat conduction in the medium (parameters that can be calculated or measured in a static phantom), but it is also to a large extent dependent on the blood flow via the complicated vascular network, a factor that is not known in detail in the actual clinical case.

Phantoms can, however, be of great value, e.g. for studying and comparing absorbed power distributions from different heat-sources. Data on different phantom materials have been tabulated by Stuchly and Stuchly (1980). The most widely used muscle-equivalent phantom is that originally described by Guy (1971). It consists of a mixture of water, polyethylene powder, salt and a gelling agent (TX-150 or "super-stuff" from Oil Center Research, Lafayette, Louisiana, USA).

This phantom material was first used in the present study but it proved to be difficult to mix, especially to get the polyethylene powder homogeneously distributed in the mixture. On the proposal of the "Swedish Institute for Food Preservation Research", the polyethylene powder was replaced by sugar. Since then, only this type of phantom material has been used for simulating muscle tissue. The composition of the phantom is: saline solution (60.0%), sugar (22.5%) and TX-150 (17.5%). The conductivity of the material is governed by the NaCl-concentration. The real, ϵ_r' , and imaginary, ϵ_r'' , parts of the complex permittivity for the

phantom material, were measured with an open-ended coaxial line technique similar to the method described by Athey et al. (1982). The measurements were performed at the Institute of Microwave Technology, Sandkullen, (for 915 MHz), and at the Department of Electronphysics II, Chalmers University of Technology, Gothenburg, (for 2450 MHz).

The data for 915 MHz are shown in Figure 8 and for 2450 MHz in Figure 9 as a function of the NaCl-concentration of the saline solution. This phantom material (containing sugar) is considered much easier to manufacture than the phantom according to Guy. It was also possible to store the phantom material for long periods

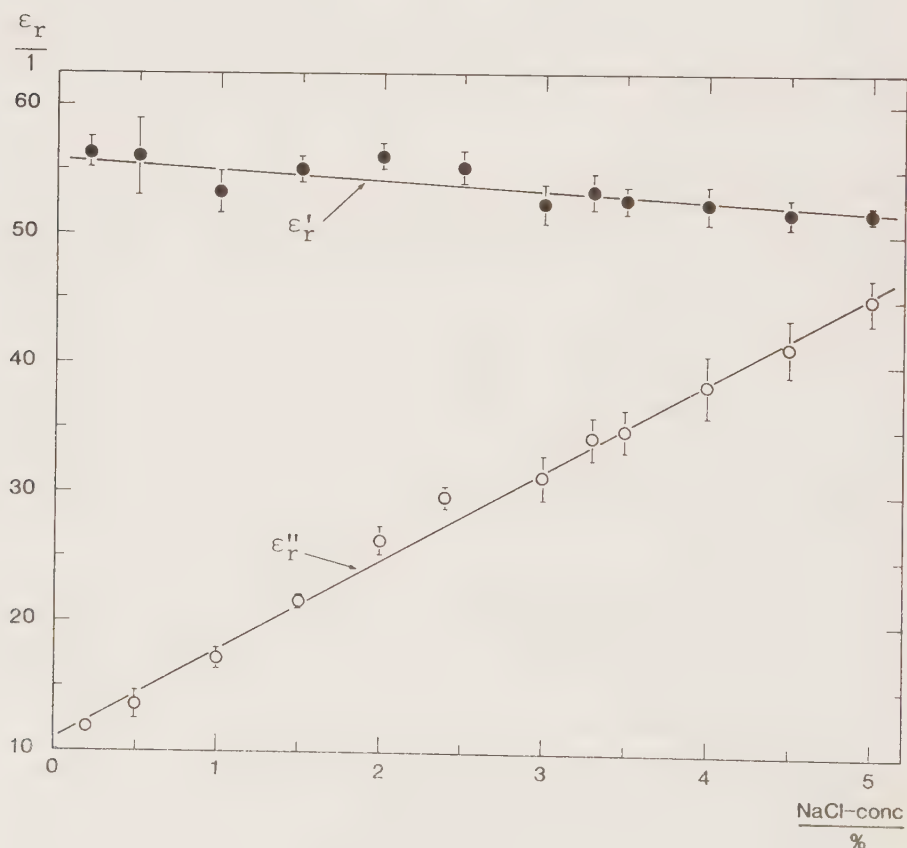


Fig. 8. Permittivity as a function of NaCl-concentration for the muscle phantom, measured at 915 MHz. (The bars indicate ± 1 S.D. of 10 measurements in different parts of a phantom block).

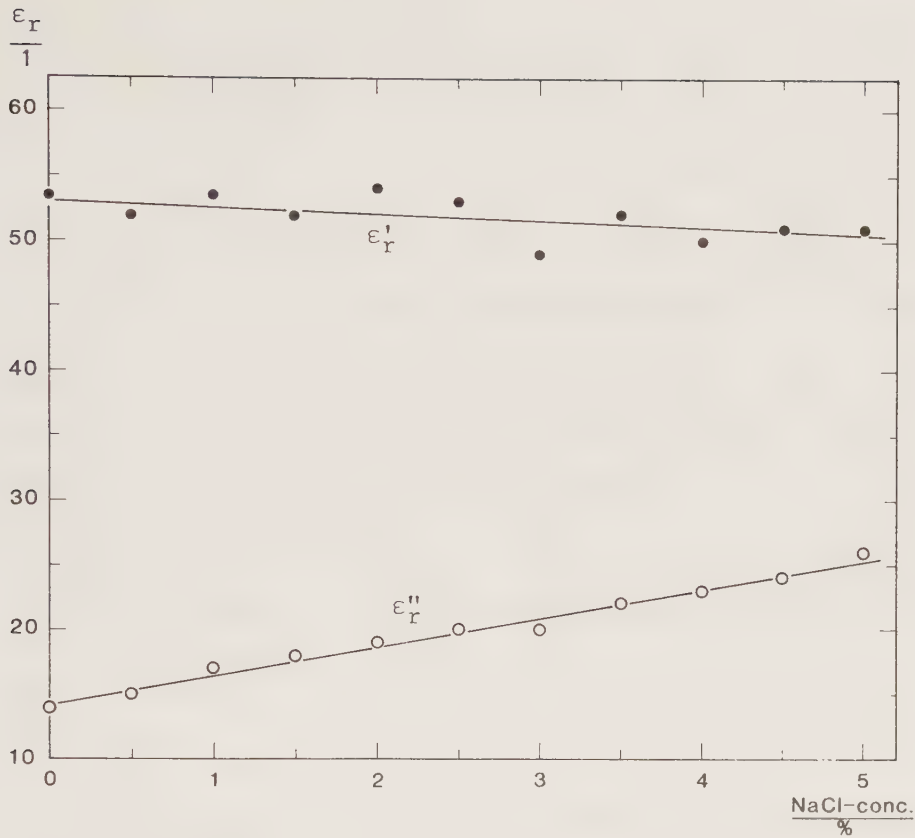


Fig. 9. Permittivity as a function of NaCl-concentration for the muscle phantom, measured at 2450 MHz.

Table I. Properties of the muscle equivalent phantom.

f MHz	NaCl-conc %	$\frac{\epsilon'_r}{1}$	$\frac{\epsilon''_r}{1}$	$\frac{\sigma}{\text{Sm}^{-1}}$	$\frac{d_s}{\text{mm}}$	$\frac{\lambda}{\text{mm}}$
2450	1.0	52	16	2.18	18	17
915	2.5	54	28	1.43	28	43

of times (several months) without any changes in its dielectric properties. The specific NaCl-concentrations used and the resulting dielectric properties are given in Table I.

The use of the phantom material is described in Paper II for measuring the absorbed power distribution for the applicators used in the 915 MHz hyperthermia system.

The fatty tissue phantom developed by Guy (1971), based on a laminac polyester resin, has not been as widely used as has the muscle phantom, due to the difficulties in making it, and the impossibility of modelling it. A new phantom, simulating fatty and bone tissues, that does not have these disadvantages, is under development (Lagendijk and Nilsson, to be published).

5.6. Dual applicators

One problem in the clinical hyperthermia treatments has been to obtain therapeutic temperatures at the tumour periphery and adequate deep heating. Anatomical topography often permits the application of two tilted applicators, e.g. in the head and neck area, on extremities and on large protruding tumours. Theoretical calculations of the absorbed power distribution from such an applicator configuration were performed in a homogeneous muscle equivalent medium (Paper III). The use of two applicators, excited coherently in phase at the lower microwave or upper radiofrequency band, can considerably improve the absorbed power distribution. Both the depth penetration and the lateral power distribution are superior compared to those of a single applicator or two applicators excited non-coherently.

6. CLINICAL APPLICATIONS

Preliminary clinical results are reported in Paper IV. During the period August, 1980, - January, 1984, 45 patients with superficial tumours (maximum depth of about 3 cm) have been treated with a combination of hyperthermia (induced with either 2450 MHz or 915 MHz microwaves) and radiation therapy (x-rays, ^{60}Co -gamma or electron beams). Due to experience from the early clinical treatments, the extensive treatment schedule described in Paper IV was reduced to the fractionation schedule for the combined treatment shown in Table II. In patients with multiple tumours, one lesion was treated with only radiotherapy, which makes it possible to compare the different treatment modalities, the patient himself serving as a control. In such cases, the smallest tumour has usually been treated with radiotherapy alone.

Table II. Fractionation schedule for combined radiotherapy (RT) and hyperthermia (HT), shown for one out of two identical weeks .

	Day 1	Day 2	Day 3	Day 4	Day 5	
RT (3.00 Gy, totally 30.0 Gy)	x	x	x	x	x	(x 2 weeks)
HT (41-45 °C, 45 min)		x			x	(x 2 weeks)

A follow-up was performed in January, 1984, which included 33 evaluable patients with 72 lesions treated in accordance with the schedule in Table II. At the time of treatment, these patients had superficial, local recurrences of tumours or metastases in

spite of established treatment received earlier. All of the patients received low-dose radiotherapy (3.00 Gy x 10 fractions during 2 weeks). Hyperthermia (41-45 °C for 45 minutes) was given 3-4 hours after radiotherapy twice a week, i.e. four sessions (Table II). The results are presented in Tables III and IV.

Table III. Results in the whole patient series (72 superficial tumours in 33 patients).

	R e s p o n s e			Duration (months)	
	CR [#]	PR [*]	CR+PR	Interval	Median
HT+RT	20/51	17/51	37/51	2-39+	5
			p<0.05		
RT	6/21	4/21	10/21	1-12+	3

[#]CR = Complete remission, ^{*}PR = Partial remission

Table IV. Results in 17 patients with two or more superficial tumours (totally 53), the patient himself serving as a control.

	R e s p o n s e			Duration (months)	
	CR	PR	CR+PR	Interval	Median
HT+RT	18/32	9/32	27/32	2-29	6
			p<0.01		
RT	6/21	4/21	10/21	1-12+	3

The response rate (CR+PR) was significantly better for the combined treatment modality. A chi-square test resulted in the

significance levels $p < 0.05$ for the whole patient series (Table III) and $p < 0.01$ for the patients with their own control tumours (Table IV). It should be recalled that the absorbed radiation dose that was possible to give in the treatment of these recurrences was quite low, since the patients had earlier usually received high absorbed doses in the same areas. For these patients, however, the addition of hyperthermia to radiation has been beneficial.

Large temperature gradients have often been observed during the hyperthermia treatments. The amounts of microwave power needed to heat the tumours have also varied considerably. As mentioned earlier, the blood flow is the major factor governing the amount of power needed to heat a tumour. The time-temperature plot shown in Paper II, Fig. 7, is from a patient with a small (about $3 \times 3 \times 2.5 \text{ cm}^3$) superficial metastasis on the chest wall, from a mammary carcinoma. The nodule was treated with 915 MHz and about 110 W of incident power, using a $9.4 \times 9.4 \text{ cm}^2$ applicator. This case was compared to a hyperthermia treatment of a large (about $8 \times 6 \times 5 \text{ cm}^3$) recurrence of a mammary carcinoma. This large tumour was treated with the $18 \times 12 \text{ cm}^2$ applicator, with an average net power of 90 W. The SAR-value on the central axis for this applicator is about 60% of the SAR-value for the $9.4 \times 9.4 \text{ cm}^2$ applicator, with the same amount of incident power. The tumour temperature range measured was about 42°C to 45°C in both cases, with a surface temperature of about 41°C for the small tumour and about 42°C for the large tumour, since the latter also involved the skin. To estimate the magnitude of the blood flow in these two lesions, the thermal washout-curves (the cooling part of the time-temperature plot) were analyzed. To avoid influence from the surface temperature control, the temperature data from the thermistor probes located at depths greater than 10 mm were used. The analysis was made during the first 60 seconds after the microwave power was turned off. If it is assumed that the thermal conductivity and the metabolic heat generation are small compared to the heat elimination via the

blood perfusion, and that $\rho_b = \rho_t$, $c_b = c_t$ and $(T_a - T) = \Delta T$, the bio-heat transfer equation (Equations 33 and 34) can be simplified to:

$$\frac{\delta T}{\delta t} = w \Delta T \quad (37)$$

and thus:

$$\Delta T = \Delta T_o e^{-wt} \quad (38)$$

where w is the blood-perfusion rate.

This relationship did not, however, fit the thermal washout-curves studied. Jain (1980) proposed that a factor, η , which described the effectiveness of heat transfer between the tissue and the venous blood, should be included in the perfusion term:

$$q_b = \eta w \rho_b c_b (T_a - T) \quad (39)$$

Milligan et al. (1983) proposed the relation:

$$\eta = \left(\frac{\Delta T}{\Delta T_o} \right)^z \quad (40)$$

where z is empirically determined from the temperature clearance data. This results in the expression:

$$\Delta T^z = \frac{\Delta T_o^z}{1 + zwt} \quad (41)$$

Milligan et al. (1983) obtained a good correlation using this expression on thermal washout-curves measured in canine muscle. This relation was also found to fit the temperature washout-curves from the two patient treatments during the 60 seconds interval studied. This expression was thus used for an estimation of the blood-perfusion rates at the measurement points in the

tumours. The results are shown in Table V.

Table V. Blood-perfusion rate, w (min^{-1}) measured by thermal clearance according to Equation 41.

Treatment No.	Small tumour	Large tumour	
	Centrally at 13-15mm depth	Centrally at 15 mm depth	30 mm from centre at 30 mm depth
1	0.65	--#	0.35
2	0.66	0.25	0.34
3	0.59	0.30	0.38
4	0.69	0.27	0.33
(Unit: min^{-1})			

#Thermistor failure during treatment

According to these calculations, the blood-perfusion in the small tumour is thus about twice the perfusion in the large lesion, which is in good agreement with the higher absorbed power needed to heat the smaller nodule to approximately the same temperature level. The differences in the calculated blood-perfusion rates at a specific location are remarkably small for all of the treatment sessions, indicating no change in blood circulation throughout the two-week hyperthermia course for these particular tumours.

The limitations of the bio-heat transfer equation have been described earlier (Chapter 4). Measurements of perfusion rates with this technique may thus be uncertain but the method might enable the estimation of blood-perfusion rates in connection with hyperthermia treatments.

7. SUMMARY AND CONCLUSIONS

The computerized hyperthermia system has shown to be well suited for the clinical treatment of superficial tumours. The tumours most difficult to heat have been those located in the head-and-neck area. This fact is due to the irregular patient contour in this region, resulting in poor coupling of the applicator to the patient. The introduction of 915 MHz has considerably improved the treatments, compared to 2450 MHz. This is a result of the larger penetration depth at 915 MHz, and the possibility of coupling the electromagnetic field at this frequency with a temperature controlled water bolus. 2450 MHz has often given moderate to severe pain during the treatment. Necroses in normal skin have occurred, probably due to "hot spots" (IV). Using 915 MHz, these side-effects have almost completely disappeared.

The use of temperature sensors with metallic leads necessitates a pulsed irradiation technique with temperature readings during the power-off state (I, II). The magnitude of the interaction between the electromagnetic field and the temperature probe is highly dependent on the location of the probe compared to the direction of the electric field in the tissue.

Guy and Lehmann (1966) proposed the optimal frequency to be 750 MHz, with a direct contact applicator for heating areas of 100 - 200 cm². This was based on calculations and measurements of absorbed power distributions in a three-layer (skin-fat-muscle) configuration where the aim was to keep the ratio of fat/muscle heating as low as possible. The frequency 915 MHz, however, was shown to be almost equivalent in this respect. Scott et al. (1983) used 2450 MHz, 915 MHz and 434 MHz in their hyperthermia treatments, and concluded that 915 MHz was the most useful frequency from a clinical point of view.

By lowering the frequency, the penetration depth of a plane wave

increases. This increase is, however, marginal when applicators of clinically convenient size are considered (III). Where the anatomical patient contour permits the use of two tilted applicators, and if these in addition are excited coherently in phase, both depth penetration and lateral power distribution can be considerably improved, as shown in Paper III. The frequency of 915 MHz is, however, not optimal for this case, due to its rather short wavelength in tissues with high water content. A more suitable frequency would be 434 MHz or lower (III). Equipment based on these findings is under development for use in clinical hyperthermia.

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TECHNIQUE FOR MICROWAVE-INDUCED HYPERTHERMIA IN SUPERFICIAL HUMAN TUMOURS

P. NILSSON, B. PERSSON, E. KJELLÉN, C.-E. LINDHOLM and T. LANDBERG

The renewed interest in hyperthermia as a treatment modality of malignant tumours has created a need for clinical heating equipment able to induce controlled elevated temperatures at depth in tissue for a prolonged time period.

At present the main techniques for inducing local hyperthermia are electromagnetic heating with different induction techniques and ultrasound heating (HAND & TER HAAR 1981).

Different techniques based on microwaves are frequently used clinically for inducing hyperthermia in superficial tumours (MENDECKI *et coll.* 1978, ARCANGELI *et coll.* 1980, U *et coll.* 1980, LUK *et coll.* 1981, PEREZ *et coll.* 1981).

The main problem in hyperthermia treatment is thermal dosimetry. Non-invasive temperature measurement techniques, e.g. radiometric methods (N'GUYEN *et coll.* 1980) and methods based on the dependence of ultrasound velocity on the tissue temperature (NASONI *et coll.* 1979) are under development but not yet applicable in clinical routine. Thus, at present the method of choice for temperature monitoring is direct measurement of the tissue temperature by invasive techniques.

In order to generate hyperthermia in superficial tumours a system was constructed using a 2450 MHz microwave generator as the heating source and commercially available thermistor probes for temperature measurement. One of the difficulties when using microwaves is the interaction between the electromagnetic field and the metallic wires of

the thermistor probe. In order to avoid this completely, a temperature reader without metallic parts is desirable. Several types of non-perturbing probes have been developed (CHRISTENSEN & DURNEY 1981) and some are now commercially available. These temperature probes have in our opinion, however, too large diameters and are too expensive for use in clinical routine.

In order to overcome these problems a computer control system based on invasive temperature control with conventional thermistor probes has been built. The present system for inducing local hyperthermia in superficial tumours in patients is a further development of an equipment previously constructed in this department of radiation physics for inducing controlled hyperthermia in small mammals (NILSSON *et coll.* 1980, BOLMSJÖ *et coll.* 1982). Up to now the system has been used for hyperthermia treatment of more than 20 patients with different kinds of superficial tumours in combination with ionizing radiation. Preliminary clinical results are reported by LINDHOLM *et coll.* (this issue, p. 241).

Material and Methods

The hyperthermia system is shown in Fig. 1.

The microcomputer (based on the S-100 bus) is provided with the 8-bits microprocessor Intel 8080A (Intel Corp., USA) and 48 kbyte of read/write mem-

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ory. The dual floppy drive has a total of 630 kbyte of formatted storage. The microcomputer is connected via an interface to a 2450 MHz microwave generator (Siemens Radiotherm 305) with a maximum output power of 200 W. The microwave power is fed through a coaxial cable to a bi-directional coupler (Narda Microwave Corp., USA, model 3022) which makes it possible to measure the incident and reflected microwave power.

The microwave power is transferred to the patient by a circular air-filled waveguide with a diameter of 90 mm. The waveguide is excited in the TM_{01} -mode. In order to obtain a circular polarized electric field, the microwave power is divided by a coaxial 90° -hybrid junction (Narda model 3033) and fed through 2 coaxial lines to the applicator. A quarter wavelength transformer is placed at the applicator surface to minimize the reflected power from the patient.

The applicator is provided with a system for cooling of the skin surface. The impedance transformer is furnished with a grid of small air channels through which compressed air flows (Fig. 1).

For temperature registration intravenous cannulas (Venflon, 18 gauge, diameter 1.2 mm) are inserted into the tissue. The metallic needles are withdrawn and replaced by thermistor probes (Yellow Springs Inc., USA, model 511) with a diameter of 0.6 mm. Besides, at least one thermistor probe is placed on the skin of the patient.

The thermistor probes are connected to a temperature registration unit containing bridge circuits, instrumentation amplifiers and a multiplexed 12-bits analogue to digital converter. A total of 8 probes can be used simultaneously. The digitized temperature signals are sent to the microcomputer for calculation of temperature and for control of the heating session.

Via the terminal, input data such as patient data, preset temperature, hyperthermia treatment time, thermistor identification numbers are transferred. Thermistor calibration data are fetched from the diskette according to the thermistor numbers used. All information is then stored for documentation in the patient file on a floppy diskette. Before the hyperthermia session starts all temperature probes are read and stored on disk every fifteenth second for a preset time period.

One of the thermistors (usually the one situated in the centre of the tumour) is chosen as the master thermistor. The temperature recorded at this probe

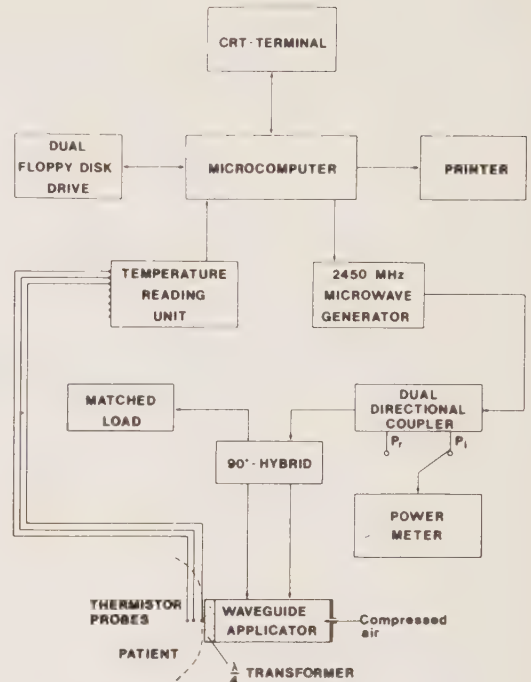


Fig. 1. Diagram of the hyperthermia system.

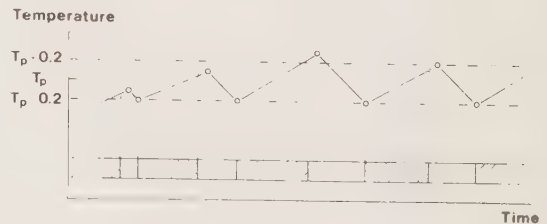


Fig. 2. Principle for the hyperthermia control algorithm. Microwaves on, 10 to 20 s (■). Microwaves off (□). Temperature ($^{\circ}\text{C}$) reading (○). Time in minutes.

is compared with the preset temperature value. The principles of the control algorithm are shown in Fig. 2. If the temperature at the master thermistor is less than the preset temperature minus 0.2°C , the heating is started by a signal from the computer to the microwave generator.

During the microwave pulse, which has a start value of 15 seconds, temperature and time data are displayed on the terminal and stored in the patient file on diskette. Two seconds after the microwaves have been shut off by the computer, all thermistor probes are read 'simultaneously', e.g. during a time

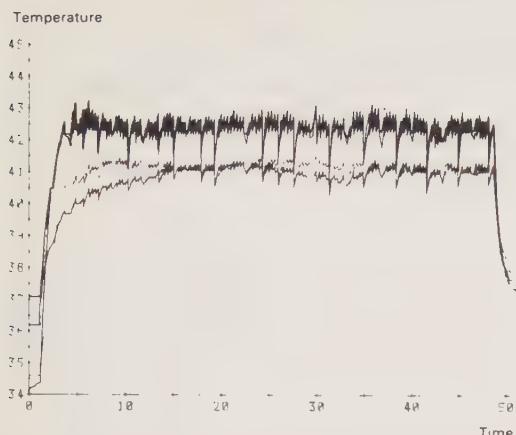


Fig. 3. Example of temperature ($^{\circ}\text{C}$) profiles at patient treatment. Black: Centrally at 7 mm depth in tumour. Red: Centrally on the skin. Blue: Centrally at 20 mm depth in tumour. Green: Peripherally at 4 mm depth in normal tissue. Time in minutes.

period of less than a few milliseconds. Temperature data are updated on the terminal and on the diskette and a new cycle is started by reading the temperature at the master thermistor. The microwave power is selected manually to attain a temperature increase of approximately 0.5°C during a 15 seconds microwave pulse.

When the preset temperature value is reached the length of the microwave pulse is adjusted by the control program (Fig. 2). Thus, the temperature at the master thermistor will theoretically fluctuate between $T-0.2^{\circ}\text{C}$ and $T+0.2^{\circ}\text{C}$.

When the hyperthermia period is out, the cooling of the tissue is followed during a preselected time period by temperature reading every fifteenth second.

Results and Discussion

The effective absorption of 2450 MHz microwaves in tissue allows for treatment of superficial tumours only. The penetration depth for a plane wave, e.g. the depth at which the power density is reduced to $1/e^2$ (13.5%) of its value at the surface, is 1.7 cm and 11.2 cm in muscle and fatty tissue, respectively, at 2450 MHz (JOHNSON & GUY 1972).

It would be desirable to be able to plan the temperature distribution in the treatment volume with the same accuracy as the absorbed dose in radiation therapy. However, this is not yet practically possi-

ble due to a number of factors influencing the true temperature distribution. Heterogeneous tissues have very complex absorption patterns of microwave radiation due to different dielectric properties which are related to the water content in the tissues. Standing waves may appear due to reflexions at tissue boundaries resulting in local 'hot spots'. This may present a problem, e.g. for subcutaneous fat, at the frequency used due to its short internal wavelength in tissue. Heat is transferred in tissues mainly by conduction, defined by the thermal conductivity coefficient, and by blood flow. The heat transport by blood flow plays an important role in modifying the temperature distribution (PATTERSON & STRANG 1979, BOWMAN 1981). Thus, a thermal dose-planning requires accurate knowledge of the blood perfusion in the entire heated volume. Blood flow velocities may besides be different in normal tissue and solid tumours. Furthermore, the flow rates may change during the hyperthermia session due to physiologic parameters and other effects such as disturbances of the microcirculation caused by the forced elevated temperature (EDDY 1980).

The influence of the blood flow has been noted in the wide range of microwave power needed to induce hyperthermia. In some tumours, temperatures within a therapeutic interval (about 41°C – 44°C) have been obtained at depths up to 3 cm with moderate microwave power levels. In other cases it has been impossible to achieve this temperature at depths lesser than one cm without excessive heating of the skin.

A problem observed in almost all cases is the difficulty to raise the temperature at the tumour periphery to a hyperthermic level. This is mainly due to the power density distribution from the applicator which has its maximum at the centre of the aperture.

The variation in penetration depth and temperature homogeneity might also be due to variations in coupling of the microwave applicator to the patient and the shape of the outer contour of the treatment area.

Point measurements of the temperature are by no means an optimum technique for thermal dosimetry but it gives at least a rough estimation of the temperature distribution in the treatment volume. The interaction between the metallic wires of the thermistors and the electric field causes local heating in a region close to the thermistor probe and noise pickup in the electronics of the temperature reading

unit. It has been shown by BOLMSJÖ *et coll.*, using the same type of thermistors and temperature reading unit, that these effects give rise to an incorrect temperature measurement during microwave irradiation. However, this disturbance of the temperature signal declines rapidly and 2 seconds after the microwave power is switched off it has disappeared completely in a non-perfused muscle equivalent phantom. Thus, when using conventional thermistor probes with metallic wires a pulsed microwave system as described must be used.

Patient data and temperature profiles are stored on a floppy diskette and can when desired be sent to the printer for a hard copy. Temperature profiles from treatment of a patient with a tumour in the parotid gland appear in Fig. 3. As shown by this figure rather marked temperature inhomogeneities are obtained in the heated volume mainly due to the rapid absorption of 2 450 MHz microwaves and inhomogeneities in the primary microwave beam. The occasionally occurring large temperature drops during the treatment are due to patient movement resulting in an inadequate coupling between the applicator and the patient.

The hyperthermia control system and the temperature measurement technique have proven to be very reliable in clinical work. The control system can easily be interfaced to other types of heat induction methods. Microwaves at lower frequencies must be used to obtain better temperature distributions in superficial tumours and further development of microwave applicators is necessary.

SUMMARY

In order to induce local hyperthermia in superficial tumours a computer system using a 2 450 MHz microwave generator connected to a circular (diameter 90 mm) direct contact applicator was constructed based on invasive temperature control. Small thermistor probes with a diameter of 0.6 mm are inserted in the tumour and surrounding tissues. Eight thermistors can be used simultaneously and one of them is chosen as the 'master'. The automatic control system used a pulsed irradiation technique to avoid the problem with interactions between the metallic wires of the temperature probe and the electromagnetic field. With the system it was possible to control the temperature at the master thermistor within $\pm 0.5^\circ\text{C}$ from the preset value.

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COMPUTER-CONTROLLED MICROWAVE SYSTEM FOR CLINICAL HYPERTHERMIA

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Abstract

This paper describes a hyperthermia system, which has been developed for clinical use. Different direct-contact applicators working at the ISM microwave frequency of 915 MHz are used for inducing heat in superficial tumours to a depth of about 3 cm. The system is a further development of an earlier prototype, which worked at 2450 MHz. The microwave generator is controlled by a microcomputer governed by temperature measurements with thermistor probes inserted into the tissue. To minimize the influence of the interaction between the microwaves and the temperature probes, a pulsed irradiation technique is used. Until now (December, 1983), 45 patients with superficial tumours have been treated with radiotherapy combined with local hyperthermia applied by the system described in this paper.

1. Introduction

The extensive amount of biological in vitro and in vivo experimental research in hyperthermia during the last decade has established a rationale to hyperthermia as a valuable tool in cancer therapy (Field and Bleehen 1979, Law 1982). The combination of hyperthermia and ionizing radiation seems especially promising for clinical use (Overgaard 1981), but heat in combination with cytotoxic drugs is also under investigation (Dahl 1983).

The fundamentals of different heating methods for producing hyperthermia have been described by Christensen and Durney (1981), Hand and ter Haar (1981) and Hunt (1982), among others. Electromagnetic couplings of different types have proven to be an efficient method for producing therapeutic heating in tissue (Guy et al 1974). A number of authors have reported on the therapeutic efficiency of microwave-induced hyperthermia combined with radiation therapy (Arcangeli et al 1983, Fazekas and Nerlinger 1981, Hofman et al 1983, Luk et al 1981, Perez et al 1983, Scott et al 1983, U et al 1980).

In this work, we have used microwaves at the ISM (Industrial, Scientific and Medical) frequency of 915 MHz to induce local hyperthermia in superficial malignant tumours into which small temperature sensors can readily be inserted. The system is a further development of earlier equipment based on 2450 MHz microwaves for applying hyperthermia in experimental animals (Bolmsjö et al 1982) and in patients (Nilsson et al 1982).

2. Material and methods

2.1. Hardware

2.1.1. The computer system

A block diagram of the hyperthermia equipment is shown in figure 1. The computer system is based on an S-100 bus microcomputer provided with an eight bit-microprocessor (INTEL 8080A) and 64 kbyte of read/write memory (RAM). A dual floppy drive (Micropolis 1054) with a total storage of 2x300 kbyte serves as software and data file memory. For obtaining hardcopies, a matrix printer and a multi-pen plotter are incorporated. A colour monitor (NEC JC-1202 DH(E)) shows temperature data in real time during hyperthermia treatments. The colour monitor is interfaced to the computer by two graphic-display S-100 boards (Matrox ALT-512), resulting in eight colours and a resolution of 256x256 pixels. All other I/O units are either connected to the microcomputer by serial RS-232 or by parallel eight bit I/O ports.

2.1.2. The microwave system

The radiofrequency/microwave generator (MCL, Model 15222) consists of a mainframe and interchangeable RF oscillator modules ("plug-ins") covering the frequency range of 10 MHz to 2500 MHz. The plug-in used in this work is tunable from 400 MHz to 1000 MHz, and covers the two ISM frequencies of 434 MHz and 915 MHz. The unit delivers a maximum output-power of 100 W CW. The frequency used in the patient treatments has been 915 MHz.

The microwave power is fed through a coaxial cable to the applicator via a power meter (Bird Thruline Wattmeter, Model

4381-832) and a triple stub tuner (Maury Microwave, Model 1878A). The power meter, which is interfaced to the computer, measures several parameters, such as forward and reflected power (mean or peak), voltage standing wave ratio, return loss, etc. With the stub tuner, any reflected power level occurring during clinical hyperthermia can be tuned out.

The microwave generator has a built-in safety interlock system which is activated if the reflected power is greater than 10 W, which necessitates a circulator. The third port of the circulator (Western Microwave, Model 27C1478) is connected to a termination (NARDA 369BN) with a maximum power-input of 175 W CW.

The microwave generator is run in the pulse mode, i.e. its power on/off states are controlled by an external +5/0 V TTL level from the computer. The average output power is controlled by varying the duty frequency from 50% to 100%, directed by the computer.

The maximum output power of 100 W limits the applicator aperture to about $10 \times 10 \text{ cm}^2$. A linear 915 MHz amplifier (RadTec PA915/220) has recently been incorporated in the system (though not shown in figure 1). The maximum output power is now 220 W, with 22 W drive power obtained from the MCL-generator, which allows for larger aperture sizes of the applicators.

2.1.3. Microwave applicators

Different aluminium waveguide applicators with square or rectangular apertures have been constructed (figure 2). They are either air-filled or loaded with a low-loss dielectric material. The waveguide applicators are excited in the fundamental TE_{10} -mode, according to a method described by Collin (1960). The characteristics of the applicators are given in table 1.

2.1.4. Surface temperature control

The microwave power from the applicator is coupled to the patient by a flexible plastic bag containing de-ionized water. The temperature of the water is controlled with a separate unit, as shown in figure 3.

One wall of a closed metallic vessel to serve as a water tank (volume 1.75 litres) has been replaced with an ordinary heat-sink profile (used for electronic components), with its flanges pointing into the container. This wall is outwardly coupled with a copper block to a thermoelectric (Peltier) module (Cambion P/N 801-2004), with a maximum rated current of 6A at 15.4 V DC. The outer side of the thermoelectric module is provided with another heat-sink profile. By choosing the magnitude and direction of the current through the module, the water can either be actively heated or cooled. The two heat-sink profiles are thermally insulated from each other with a styrofoam sheet.

The water is circulated by a rotary pump (Eheim 1018, maximal capacity 4 litres/min) through the water tank and the plastic bag, which is placed between the applicator and the patient. The temperature of the water in the tank is measured with a thermistor probe (Yellow Springs Inc., Model 402), which is connected to the temperature-reading unit.

Due to the small water volume used, the temperature of the water can be varied by several degrees (Celsius) within a few minutes. The surface temperature unit is controlled manually, by adjusting the magnitude of the current from the power supply and, if necessary, changing its direction, but it can easily be interfaced to the computer for automatic control.

2.1.5. Temperature measurements

Teflon-coated thermistor probes (Yellow Springs Inc., Model 511) with an outer diameter of 0.6 mm are used for temperature measurements in vivo. The probes are inserted into the tissue by use of intravenous cannulas (Venflon, 18 gauge). The metallic needle has been replaced by a thermistor probe. Temperature probes are inserted in the centre and the periphery of the tumour, and placed on the skin beneath the water bolus. At present, a maximum of eight probes can be used simultaneously.

The nominal resistances of the thermistors are typically 5200 ohms, 1200 ohms and 500 ohms, at 0 °C, 40 °C and 70 °C, respectively. The thermistor probes are connected to an eight-channel temperature reading-unit. The basic components of each channel are a bridge circuit and a linear instrumentation amplifier (figure 4). The amplifiers are connected to a multiplexed 12-bit analogue-to-digital converter (ADC). The ADC is interfaced to the computer through two parallel I/O ports.

Each thermistor constitutes one of the resistors in a bridge circuit, with a bridge voltage, U_b , of 200 mV. The voltage difference, U_a , at the amplifier is

$$U_a = U_b (R_T / (R_C + R_T) - 1/2) \quad (1)$$

where R_T is the resistance of the thermistor, and R_C (=1.2 kohms) is the resistance of the fixed resistors in the bridge. The relation between the ADC-signal, S , and the resistance of the thermistor is given by the equation

$$S = b_0 + b_1 \cdot R_T / (R_T + R_C) \quad (2)$$

where b_0 and b_1 are constants.

The gain of the amplifiers has been adjusted to correspond to a temperature interval of about 15 °C to 55 °C. The constants b_0 and b_1 have been calculated by replacing the thermistor with a number of precision resistors. The values of the two constants are obtained directly from figure 4. All eight channels are adjusted to yield the same values of b_0 and b_1 . The signals from all of the channels are scanned in a few milliseconds and stored by the computer for calculating temperatures in degrees of Celsius.

2.1.6. Thermistor calibration

The relation between temperature and thermistor resistance can be expressed by the thermistor equation (Steinhart and Hart 1968):

$$1/(T+273.15)=a_0+a_1\ln(R_T)+a_3(\ln(R_T))^3 \quad (3)$$

where T is the temperature in degrees of Celsius, and a_0 , a_1 and a_3 are constants. The thermistor probes have been calibrated by the manufacturer at 0 °C, 40 °C and 70 °C, i.e. the thermistor resistance, R_T , at these temperatures is known. The three constants are easily obtained for a thermistor probe by solving equation 3 for the three given temperatures.

This is performed by a calibration program run on the microcomputer every time a new thermistor probe is incorporated in the system. The constants a_0 , a_1 and a_3 are stored together with an identification number on a floppy disk for use by the hyperthermia control program.

In addition, the thermistor calibration is checked in a temperature-controlled water bath with certified mercury-in-glass thermometers or with a precision thermistor probe (Thermometrics SP-10) approved by the National Bureau of Standards, USA.

2.2. Software

2.2.1. System software

The computer is provided with the CP/M operating system (Digital Research). The implemented high-level languages are BASIC and FORTRAN (MBASIC and FORTRAN-80 from Microsoft), a macroassembler and a linker (MACRO-80 and LINK-80 from Microsoft).

The hyperthermia control program is coded in FORTRAN and assembly language routines, which are linked together. This results in a much faster and more structured source program code than, e.g., a BASIC program, and is also easier to write and debug than a program completely written in assembly language. The subroutines used in the hyperthermia control program are also used for simple and rapid writing of dedicated computer programs for, e.g., phantom studies.

2.2.2. The hyperthermia control program

The control program is multi-task structured at two priority levels. The real-time clock routine, written in assembly language, has the highest priority. A timer activates the real-time clock routine once every 0.2 seconds. The clock routine updates and displays the time once every second on the colour monitor.

A simplified flow-chart of the lower priority control program is shown in figure 5. Each block is in principal a subroutine, written either in FORTRAN or assembly language. The flow-chart program is described in more detail in the following sections.

INP DATA: Before the real-time clock is started, different input

parameters are entered via the terminal keyboard, e.g., patient-related information, treatment time and temperature, maximum allowed temperature, $T_{\max}$, thermistor identifications and locations. One of the thermistor probes is used as a "master", i.e. the temperature value of this probe, T_m , is compared to the preselected treatment temperature, T_{pre} . The calibration constants for each thermistor are read from a file on the program disk according to the thermistor identification numbers entered.

READ S,t: The real-time clock starts (RTC ON), and the time (t) and the ADC-signals (S) from all of the thermistor probes are read and stored in RAM, which only takes a few milliseconds.

MW ON: The microwave irradiation starts by a signal from the computer and with a duty frequency of 100%. The output power is manually selected on the generator to obtain an appropriate initial temperature increase rate.

CALC T: During the power-on state, the temperatures are calculated from the stored ADC-signals. According to equation 2, R_T may be obtained from the relation

$$R_T = R_C \cdot (S - b_0) / (b_0 + b_1 - S) \quad (4)$$

The R_T value is inserted in equation 3, and the temperature is calculated in degrees of Celsius for all probes.

READ P: The power, both forward and reflected, is read.

DISPLAY: Temperatures and power levels are displayed on the colour monitor, both in digits and as a time-temperature plot, and as a time-net power plot (figure 6).

STORE: Temperatures, power levels and time are stored in a matrix in RAM. The power information is stored as forward, P_f , and reflected, P_r , peak (CW) power and net power, i.e. the difference

between P_f and P_r multiplied by the duty frequency.

WAIT: All of the subroutines described are executed in a fraction of a second, and the control program is then looped through a keyboard-subroutine during a macropulse of 18 seconds in length. Through the keyboard-routine, hyperthermia parameters can be changed in real-time without interrupting the control process. With special pre-programmed keys on the keyboard of the terminal, the preselected and the maximum allowed temperatures, the treatment time and the master thermistor can be changed. The key-stroke is stored on the I/O port of the terminal until read by the keyboard-routine, so even if the computer is executing another routine at the moment the key is depressed, the instruction will always be performed. The selectable parameters are changed step-wise, e.g., temperatures are increased or decreased in steps of 0.5°C every time the special key is depressed. Through the keyboard-routine, the program, i.e. the real-time clock, can also be stopped and restarted at any time, or the hyperthermia session can be terminated and the collected data stored in a patient file on the disk.

After the microwave pulse has ended, there is a delay of two seconds before the ADC-signals are again read and a new microwave pulse starts. This delay is to allow for the decay of any effects caused by interaction between the electromagnetic field and the metallic leads of the thermistor probes.

The program-loop described continues to run until the temperature of the master probe (T_m) has reached the preselected treatment temperature (T_{pre}), or until the maximum allowed temperature (T_{max}) is exceeded by any of the probes. If the latter is true, T_{max} will be the new control temperature, and the master thermistor is automatically changed by the program.

CALC t_{heat} : From here on, the preselected treatment-time interval is counted, usually being 45 minutes. The time at which the

treatment is finished, t_{heat} , is calculated, and the program continues according to the middle column of the flow-chart, shown in figure 5.

CONTROL P: The effective power is controlled with the computer varying the duty frequency of the microwaves. This is at present done with a pulse train from a programmable timer (INTEL 8253). The 18 s macropulse is divided in short on/off states, i.e. micropulses. The length of each micropulse is 1 ms at 50% duty frequency. To avoid temperature overshoots, the duty frequency is reduced from 100% to 75% the first time the loop is run. The duty frequency is then controlled in the range of 50% to 100%, according to the temperature difference between the preselected temperature and the temperature of the master thermistor.

When the treatment time has elapsed, the cooling of the tissue is usually registered for five minutes (right column of the flow-chart in figure 5). Optional notes about the treatment can be entered using the terminal keyboard. Data are then stored in a patient file on a floppy disk, and can, if desired, be plotted on hard copy (figure 7), or it can be later retrieved for further analyses.

3. Results and discussion

3.1. Temperature measurements

3.1.1. Thermometric accuracy and precision

The 4096 digits from the 12-bit ADC cover a temperature interval of about 40 °C (15 °C - 55 °C), which is equivalent to a temperature resolution of about 0.01 °C. The deviation between the eight temperature channels is less than ± 5 digits in the whole temperature range covered, and less than ± 3 digits in the clinical temperature range of 35 °C to 45 °C.

For a fixed thermistor temperature, the signal voltage, U_a , increases with increasing bridge voltage (equation 1). It is important, however, that the current through the thermistor is so low that it not cause any significant self-heating of the probe. With a bridge voltage of 200 mV, the self-heating of the thermistor is negligible. The thermistor current at 20 °C is about 55 μ A, which corresponds to an effect of 7.5 μ W in the thermistor. At 40 °C, these values change to a current of 80 μ A and an effect of 8.0 μ W.

The overall thermometric accuracy and resolution are better than 0.1 °C, which together with the thermistor time constant of 0.2 s and the fast scan of the probes, fulfill the thermometric and temporal requirements for a clinical thermometry system as proposed by Christensen (1979): The thermometric accuracy and resolution should be about 0.1 °C, and the temporal resolution should be 1 second, or less.

3.1.2. Electromagnetic-field disturbance of temperature measurements

The main disadvantage with conventional temperature probes is the interaction between the metallic wires of the probe and the electromagnetic field.

Several types of "non-disturbing" probes have been described in the literature, and some of them are commercially available (Hochuli 1981). They all suffer, however, from at least one of the following drawbacks: Most temperature-measuring systems are single-probe units, and thus not suitable for clinical hyperthermia, where several probes are needed. Some units have thick probes and others suffer from poor long-term stability. Such equipment is also very expensive.

This leaves the choice between conventional thermocouple or thermistor probes. We have chosen thermistor probes, which require less complex electronic equipment. Analogue multiplexing technique can be used, which enables simple and rapid scanning of the probes in a multi-probe system. Thermistors are characterized by short response time and good thermometric accuracy. No reference temperature source is needed, as is the case with thermocouples. The non-linear temperature response of a thermistor does not cause any problems in a computerized thermometry system.

To test the magnitude of the disturbance from a microwave pulse of a temperature reading, a thermistor probe was placed in a static muscle-equivalent phantom ($\epsilon^* = \epsilon_0(\epsilon' - j\epsilon'') = \epsilon_0(54 - j28)$, size $25 \times 25 \times 7 \text{ cm}^3$), at 5 mm depth in the centre of a microwave field from a TE_{10} -applicator with an aperture of $9.4 \times 9.4 \text{ cm}^2$. The leads of the probe were placed at different angles to the electric field from the applicator. The phantom was heated with an 18 seconds microwave pulse of 100 W CW, and the temperature was

registered before, during and after the pulse.

The results are shown in figure 8. For $\theta=90^\circ$, i.e. when the E-field is orthogonal to the probe wires, there is no visible disturbance of the temperature signal. The most severe case, $\theta=0^\circ$, results in a disturbance of the temperature reading corresponding to a temperature of about 2°C during the whole microwave pulse. When the power is shut off, however, there is a rapid drop in the temperature signal, depicting the pick-up noise in the electronic circuits of the temperature-reading unit. This fast decay is followed by a slower decay phase, probably as a result of the self-heating of the probe. Three seconds after the end of the microwave pulse, the temperatures are within 0.1°C in all measurements, and they then decay at the same rate. The temperature values for $\theta=0^\circ$ and $\theta=45^\circ$ are slightly higher than for $\theta=90^\circ$, which may reflect the intrinsic disturbance of the electromagnetic field pattern as a result of the metal introduced in the beam.

The time interval between the end of the microwave pulse and the temperature reading has been fixed at two seconds. The temperature drop in the tissue during this short interval does not have any major influence. The most extreme case, $\theta=0^\circ$, is hardly present in clinical hyperthermia, since the thermistor probes are placed orthogonally to the E-field from the applicator. The true E-field direction is, however, never known in the tissue due to diffraction, refraction and reflection of the microwaves at tissue boundaries, and temperature readings while the power is on should thus be avoided.

In order to test if the plastic catheters influence the temperature measurements, two thermistors were placed in the same location at 5 mm depth centrally in the phantom. One of the probes was inserted through the 18 gauge catheter used in clinical hyperthermia, while the other was inserted directly. The phantom was heated with the clinical control program. No

differences in measured temperatures were observed.

3.1.3. Absorbed power distributions in phantoms

The power distribution from the different applicators was measured in the static muscle-equivalent phantom. The studies consisted of measuring the temperature gradient by thermistor probes inserted into the phantom. The thermistor wires were always located perpendicularly to the incident electric field. The phantom was heated with a short high power (about 200 W CW) microwave pulse of 20 s duration. Temperatures were continuously measured once each second during the pulse, and registered for another 10 s after the power had been shut off, to see if any significant disturbance of the temperature signal had been present.

The temperature rise during this pulse is linear, which indicates that the influence of heat conduction in the phantom can be neglected. The rate of the temperature increase, $d(\Delta T)/dt$, is then proportional to the specific absorption rate (SAR):

$$SAR = c \cdot d(\Delta T)/dt \quad (5)$$

where c is the specific heat capacity of the phantom material. The net power, P_{net} , to the applicator is also measured and the quantity

$$P = (d(\Delta T)/dt) / P_{net} \quad (6)$$

is calculated for every measuring point in the phantom, and then used for charting the absorbed power distribution.

The absorbed power distribution for the different applicators is shown in figure 9. All values have been normalized to a point at

the centre of the aperture ($x=0, y=0$) at a depth (z) of 2 mm. The absorbed power distribution parallel to the E-field (y -direction) is rather uniform due to the constant electric field strength in this direction. For the largest aperture, $18 \times 12 \text{ cm}^2$, multiple lobes are seen in the absorbed power distribution. In the direction perpendicular to the E-field (x -direction), the width of the half-power level is reduced to about 50% of the aperture width, due to the sine distribution of the E-field strength of the applicator in this direction (Hand 1982).

The power distribution as a function of depth for the three applicators is shown in figure 10. The penetration-depth is independent of the aperture sizes studied, and is slightly lower than the penetration-depth for a plane wave. The theoretical curve for a plane wave is included in figure 10 for comparison. The absolute P-values for the different aperture sizes (figure 10) at 2 mm depth are: $1.45 \text{ m}^\circ\text{CW}^{-1}\text{s}^{-1}$ ($9.4 \times 9.4 \text{ cm}^2$), $1.21 \text{ m}^\circ\text{CW}^{-1}\text{s}^{-1}$ ($12 \times 12 \text{ cm}^2$) and $0.85 \text{ m}^\circ\text{CW}^{-1}\text{s}^{-1}$ ($18 \times 12 \text{ cm}^2$). A 10 mm thick water bolus between the applicator and the phantom does not influence the penetration-depth curve. The absolute P-value, however, at 2 mm depth for the $12 \times 12 \text{ cm}^2$ applicator, decreases to $1.02 \text{ m}^\circ\text{CW}^{-1}\text{s}^{-1}$ with the water bolus.

3.1.4. Clinical treatments

The system has proved to be well suited for use in clinical hyperthermia. So far, about 200 hyperthermia treatments have been performed in 45 patients without any serious malfunctioning of the system. The automatic control of the effective power is accurate and fast enough for clinical hyperthermia.

The surface-temperature control-unit has functioned excellently. The water bag improves the applicator coupling to the patient and decreases microwave leakage. Extreme surface cooling has seldom been necessary. Most of the tumours treated have required

heating, both subcutaneously and at depth. Bolus temperatures in the range of 35 - 40 °C have usually been employed. No skin burns have so far been observed with this new system, as was the case with the 2450 MHz system (Lindholm et al 1982).

The keyboard-routine for changing parameters in real-time has proven to be very useful during the treatments. Parameters can easily be changed to optimize the temperature-distribution in the tumour.

The change from 2450 MHz to 915 MHz has considerably improved the treatment quality. The penetration depths in muscle and fatty tissues for a plane wave at 2450 MHz are 1.7 cm and 11.2 cm, respectively, while for 915 MHz, the corresponding penetration depths are 3.1 cm and 17.7 cm (Guy et al 1974). At 915 MHz, the wave-lengths in muscle (4.5 cm) and in fat (13.7 cm) are shorter, or in the same order of magnitude as the radiating aperture. This is necessary for an efficient depth-penetration in the tissue (Guy 1971, Turner and Kumar 1982). Scott et al (1983) used microwaves at 2450 MHz, 915 MHz and 434 MHz for hyperthermia treatments of superficial tumours, and found 915 MHz to be the most useful frequency.

The phantom measurements of absorbed power-distribution can only be used as a method of comparing the characteristics of different applicators. The real temperature-distribution in tissue depends on heating time and type of tissue, but mainly on the blood flow (Bowman 1982, Strang and Patterson 1980). Large temperature gradients have often been present. It is particularly difficult to heat the periphery of the tumour, one reason being the shape of the power-distribution, as shown in figure 9. An optimal power-distribution would be one that preferentially heated the edge of the tumour. We are at present building a dual applicator system based on two TE₁₀-applicators, which are driven from the same generator. The applicators can be excited either in phase, or without phase relation by switching the power between the

applicators.

The system is well suited for introducing lower frequencies due to the broad-band RF-generator used. With the same control and thermometry system, the RF-generator can be used as a signal source, with 100 W of drive power for an amplifier at a desired frequency.

Acknowledgement

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Table 1. Applicator characteristics.

Applicator	1	2	3
Aperture size, axb/cmxcn	9.4x9.4	12x12	18x12
Dielectric filling material	Stycast 36DK* $\epsilon' = 5.4$	Sylgard 170# $\epsilon' = 3.0$	air
Cut-off wavelength, λ_c /cm	43.7	41.6	36.0
Guide wavelength, λ_g /cm	21.4	30.8	79.6

* Emerson & Cuming, Inc., USA.

Dow Corning Corp., Belgium.

Figure captions

- Figure 1. Schematic block diagram of the hyperthermia system.
- Figure 2. Photograph of applicators: 9.4x9.4 cm², 12x12 cm² and 12x18 cm² aperture sizes.
- Figure 3. Surface temperature control unit.
- Figure 4. The ADC-signal from the temperature reading unit, S , as a function of $R_T/(R_T+R_C)$, where R_T is the thermistor resistance and R_C is the resistance of the fixed resistors in the bridge. The intercept of the straight line with the S -axis ($b_0=8.988E3$) and the slope ($b_1=-1.244E4$) is obtained directly from the diagram by linear regression. A schematic diagram of the basic electronics in one of the channels in the temperature-reading unit is inserted.
- Figure 5. Flow-chart of the hyperthermia control program.
- Figure 6. Colour monitor display at a hyperthermia treatment.
- Figure 7. Plotter hardcopy from a hyperthermia treatment.
- Figure 8. The measured temperature change at 5 mm depth in a muscle-equivalent phantom during and after a microwave pulse of 100 W CW for different angles, θ , between the thermistor leads and the incident electric field. The dashed line indicates the time at which temperatures are read in the clinical treatments.
- Figure 9. Absorbed power distribution parallel to the applicator aperture for the different applicators:
a) parallel to the incident electric field, and
b) perpendicular to the incident electric field.

Figure 10. Absorbed power distribution in a muscle equivalent phantom as a function of depth for the different applicators. The dashed line indicates the theoretical depth-penetration for a plane wave.

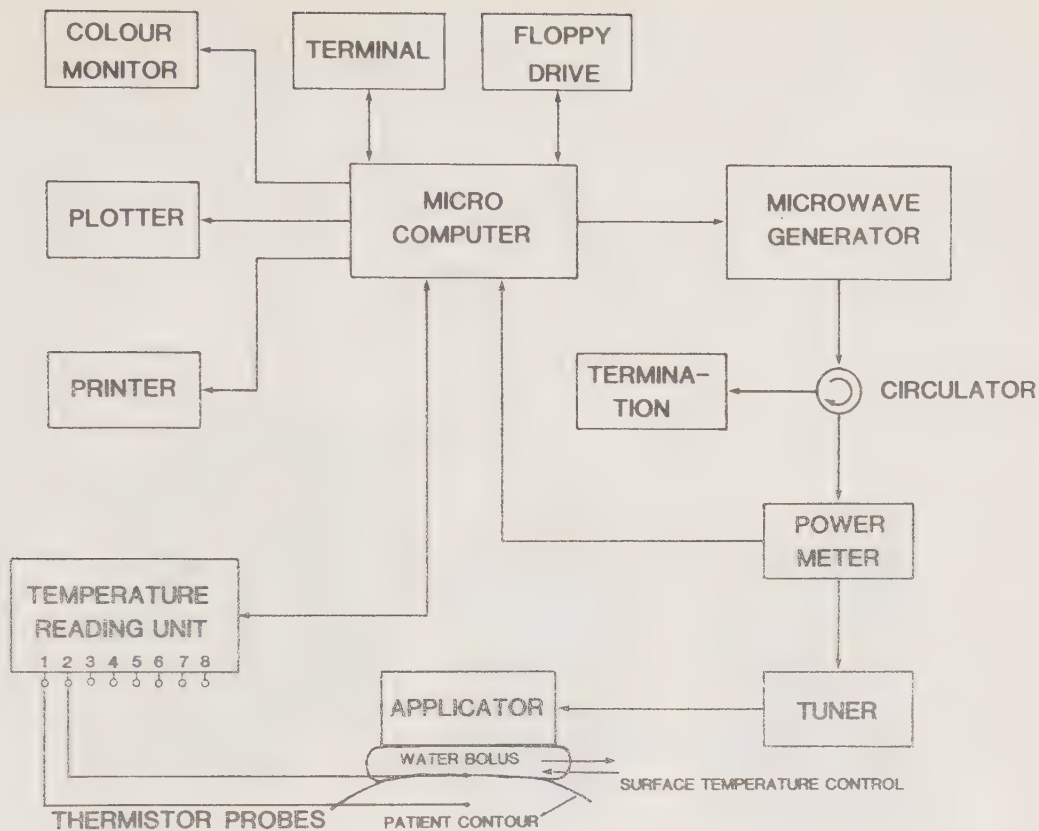


Figure 1. Schematic block diagram of the hyperthermia system.

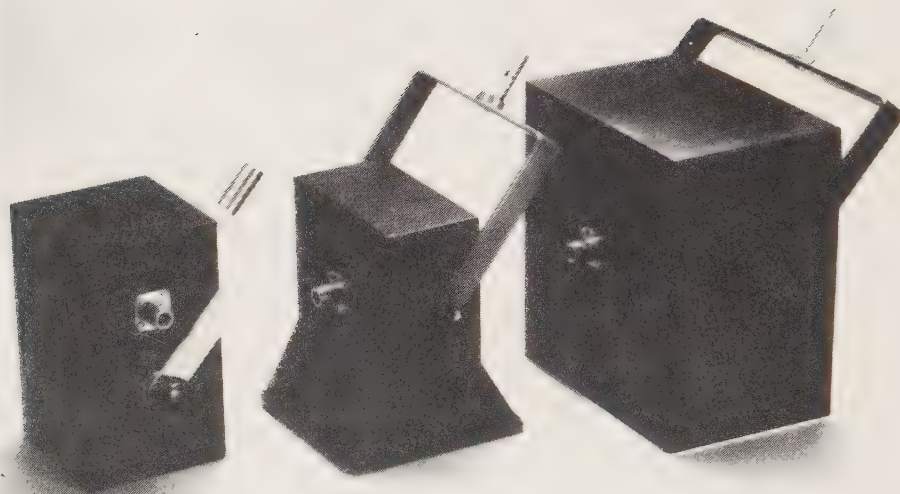


Figure 2. Photograph of applicators: $9.4 \times 9.4 \text{ cm}^2$, $12 \times 12 \text{ cm}^2$ and $18 \times 12 \text{ cm}^2$ aperture sizes.

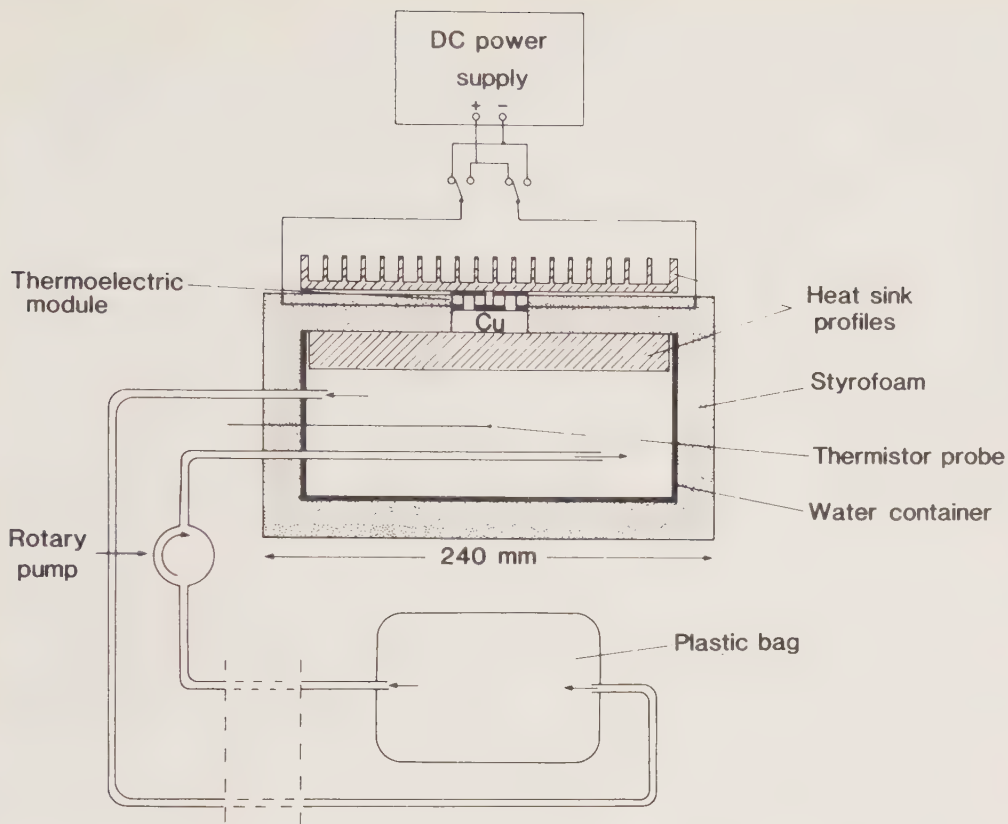


Figure 3. Surface-temperature control-unit.

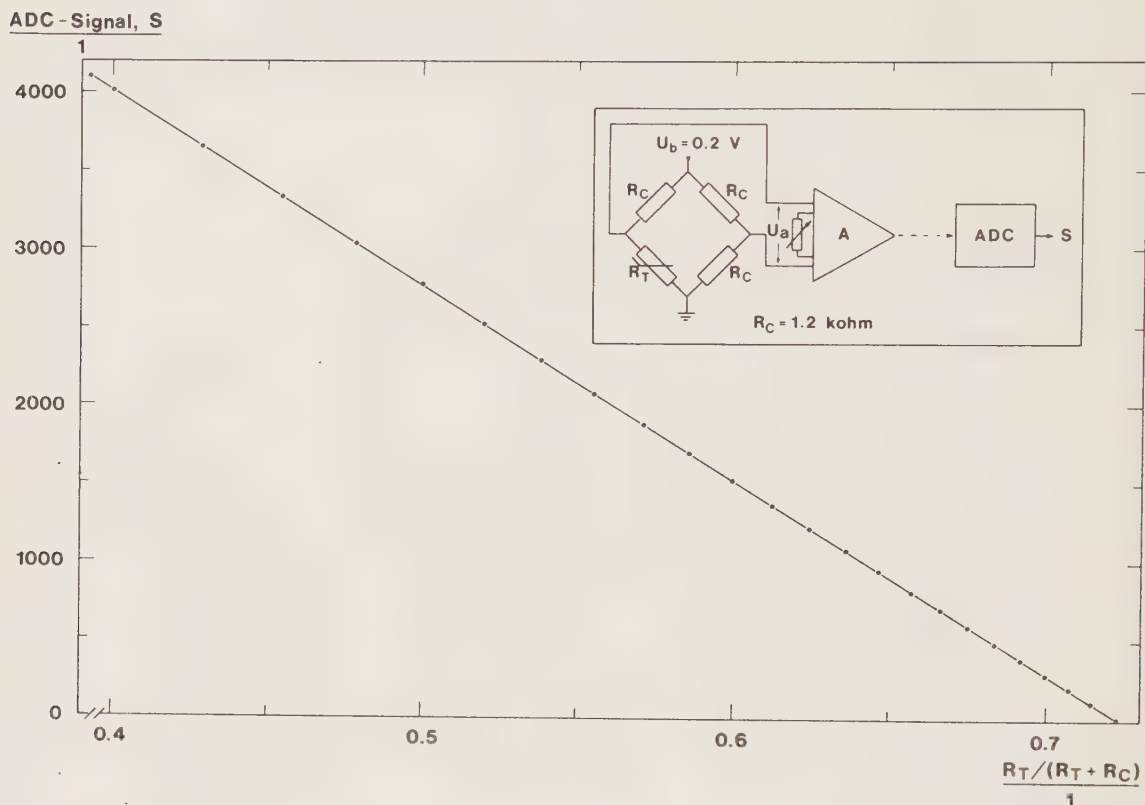


Figure 4. The ADC-signal from the temperature reading unit, S , as a function of $R_T / (R_T + R_C)$, where R_T is the thermistor resistance and R_C is the resistance of the fixed resistors in the bridge. The intercept of the straight line with the S -axis ($b_0 = 8.988\text{E}3$) and the slope ($b_1 = -1.244\text{E}4$) is obtained directly from the diagram by linear regression. A schematic diagram of the basic electronics in one of the channels in the temperature-reading unit is inserted.

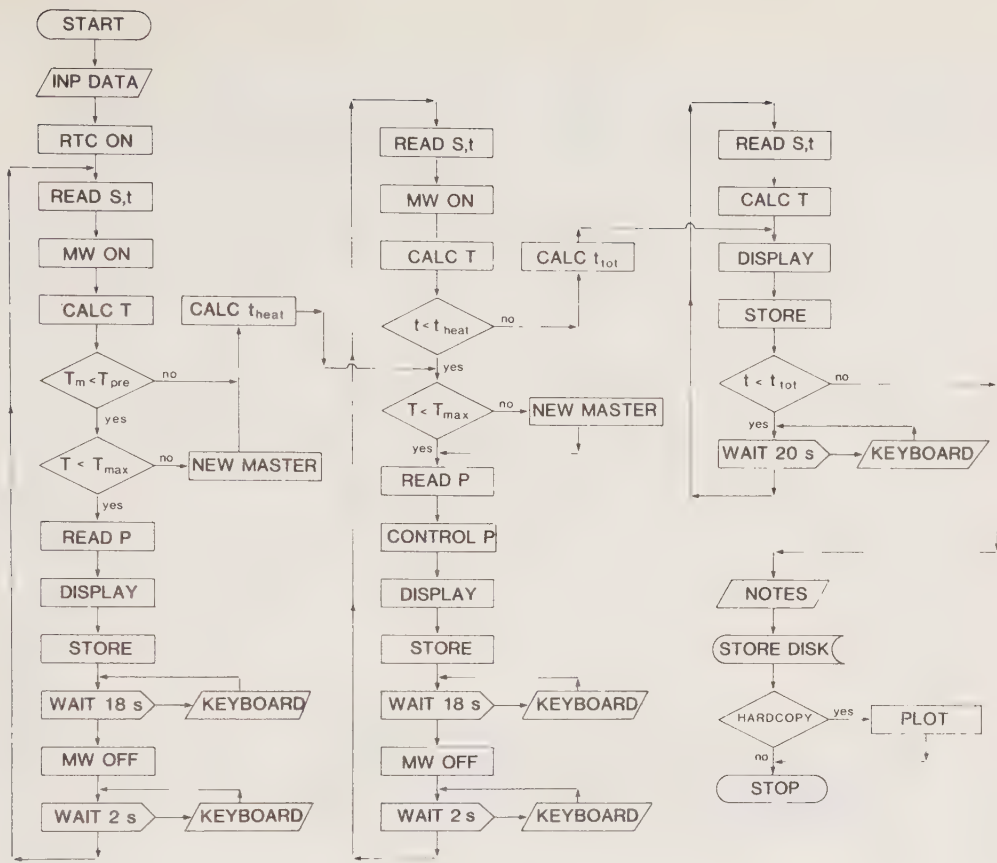


Figure 5. Flow-chart of the hyperthermia control program.

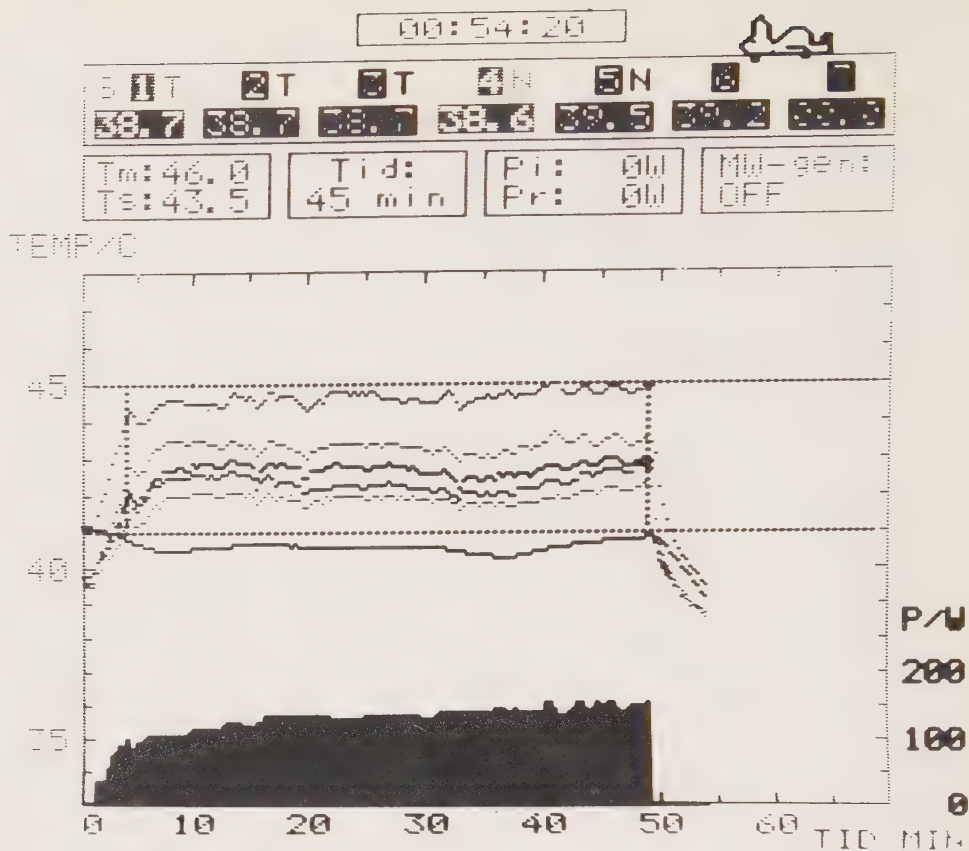


Figure 6. Colour monitor display at a hyperthermia treatment.

HYPERTHERMIA TREATMENT: OCT 25 1983
PATIENT: 123456-7890 R P
FIELD #: 8

MICROWAVE FREQUENCY: 915 MHz
APPLICATOR #: 1
TIME FOR START OF HT: 15.50
TIME FOR START OF RT: 12.00

THERMISTOR LOCATIONS:

_____ 1 (5478): 13 MM DEEP IN TUMOUR TISSUE, CENTRALLY
_____ 2 (5486): 7 MM DEEP IN TUMOUR TISSUE, 6 MM CRAN.MED
_____ 3 (5650): 11 MM DEEP IN TUMOUR TISSUE, 9 MM CAUD.LAT
_____ 4 (5651): ON THE SKIN, CENTRALLY
_____ 5 (5654): ON THE SKIN, 11 MM CRAN.MED
_____ 6 (6342): WATER CONTAINER

TEMPERATURE/C

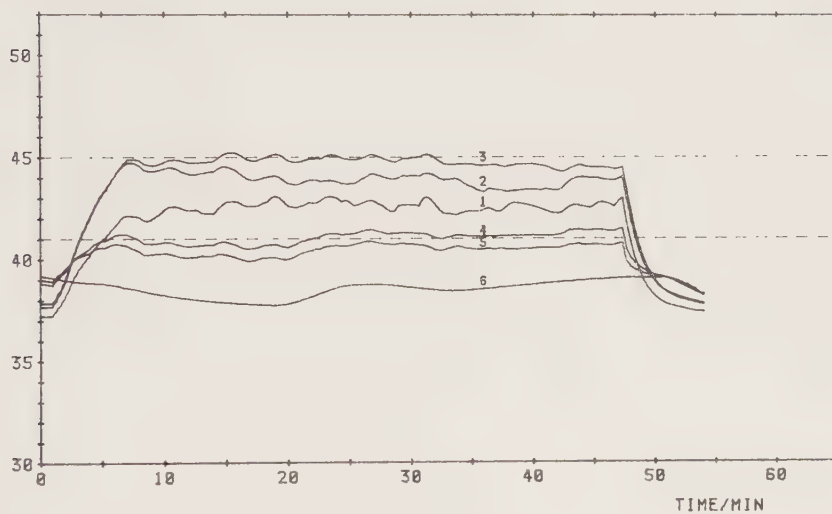


Figure 7. Plotter hardcopy from a hyperthermia treatment.

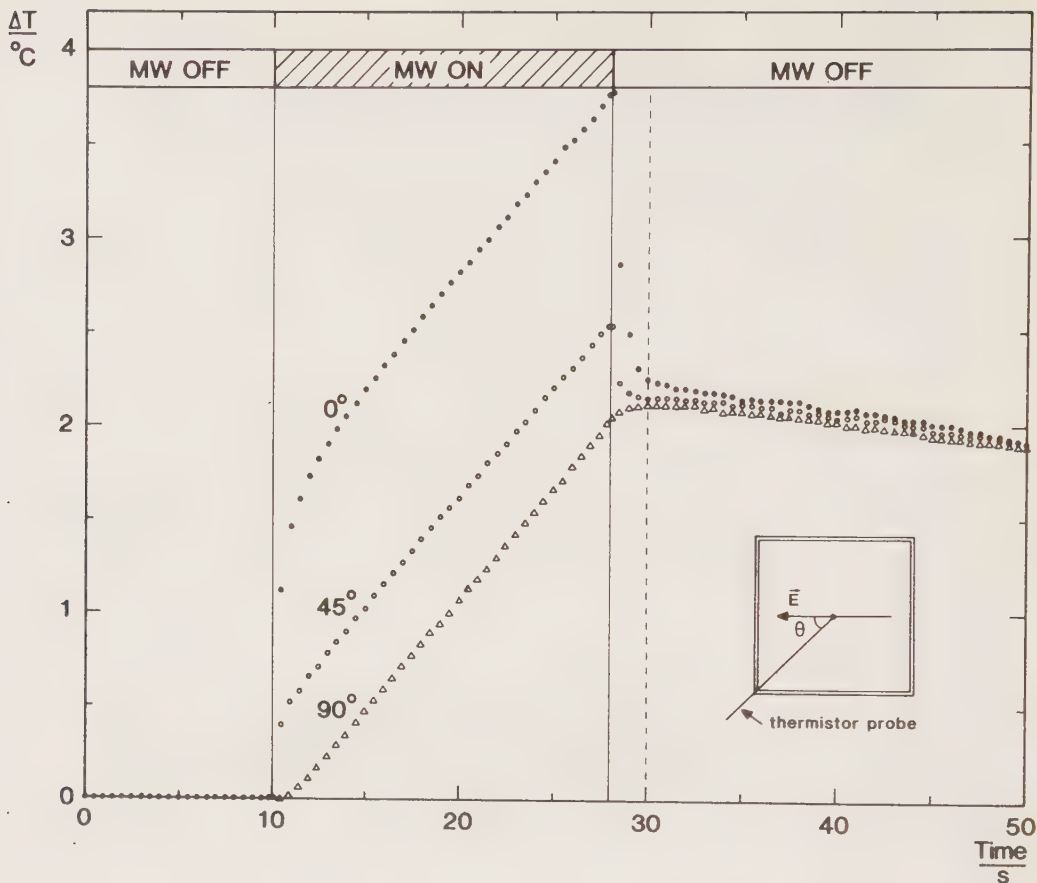


Figure 8. The measured temperature change at 5 mm depth in a muscle-equivalent phantom during and after a microwave pulse of 100 W CW for different angles, θ , between the thermistor leads and the incident electric field. The dashed line indicates the time at which temperatures are read in the clinical treatments.

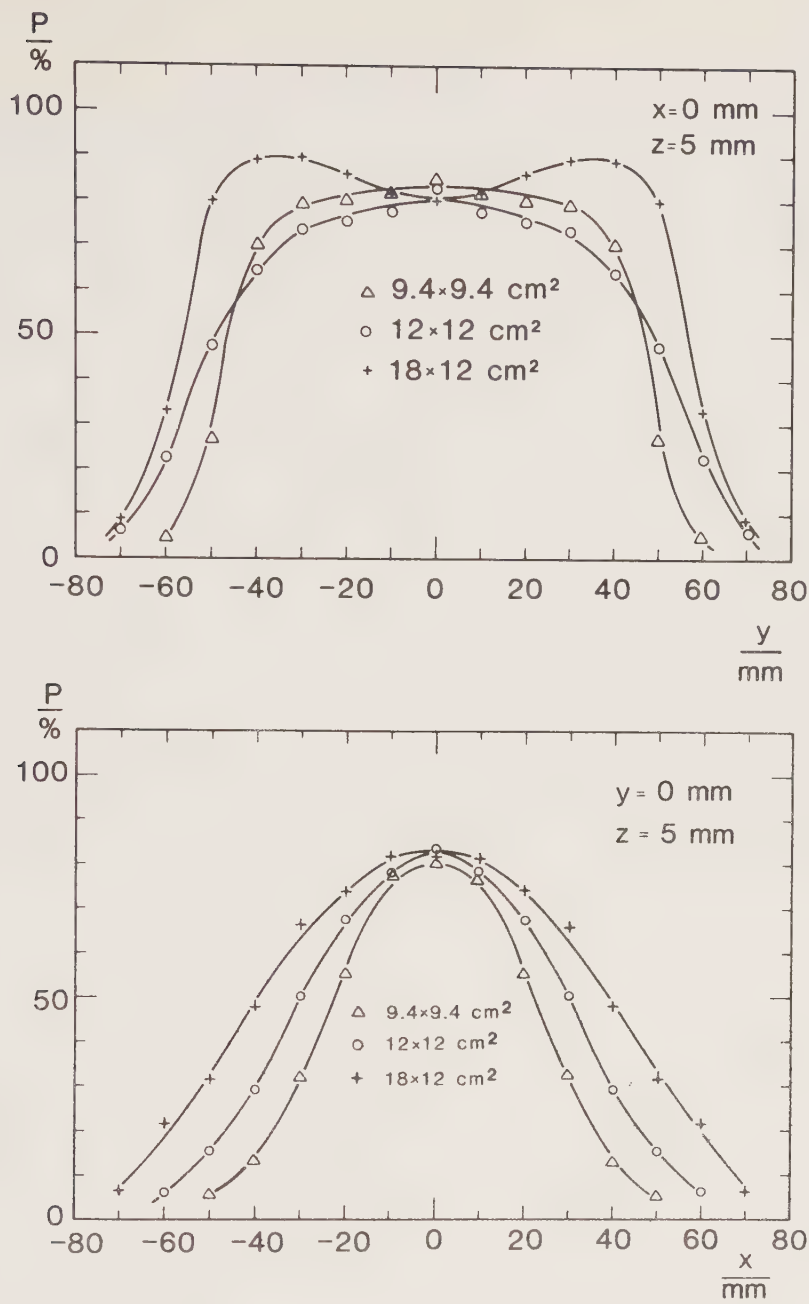


Figure 9. Absorbed power distribution parallel to the applicator aperture for the different applicators:
 a) parallel to the incident electric field, and
 b) perpendicular to the incident electric field.

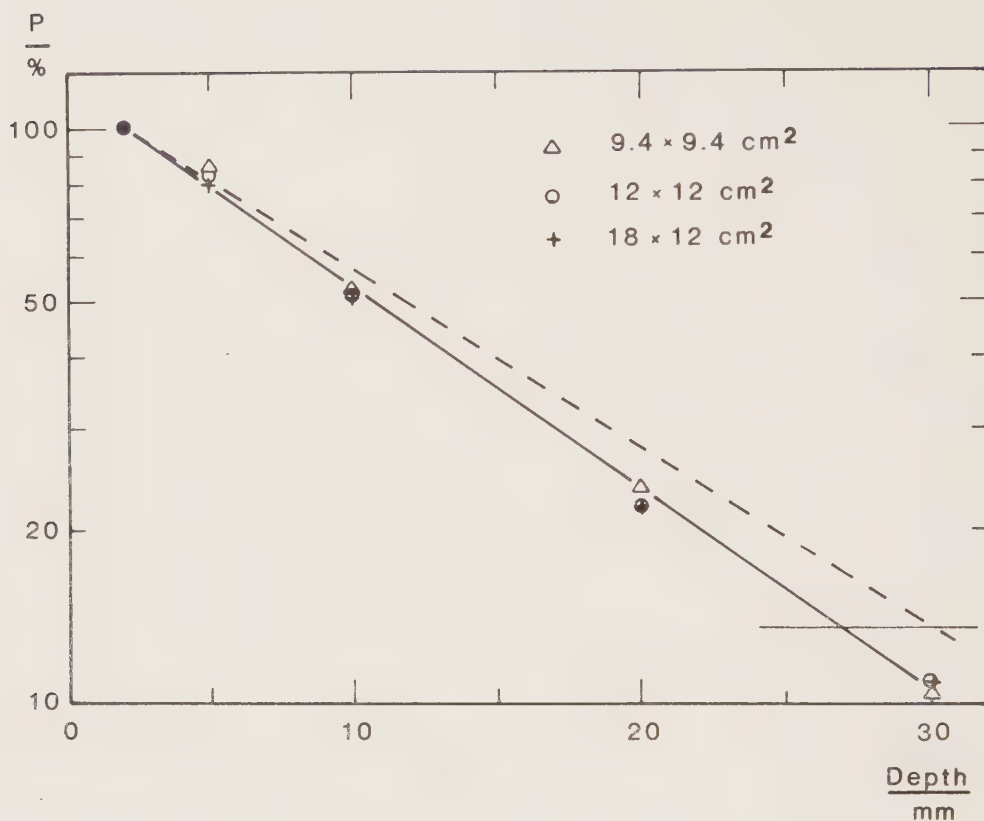


Figure 10. Absorbed power distribution in a muscle-equivalent phantom as a function of depth for the different applicators. The dashed line indicates the theoretical depth-penetration for a plane wave.

ABSORBED POWER DISTRIBUTIONS FROM SINGLE OR MULTIPLE
ELECTROMAGNETIC DIRECT-CONTACT WAVEGUIDE APPLICATORS
FOR HYPERTHERMIA

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ABSTRACT

One major problem in microwave-induced clinical hyperthermia treatment of superficial tumours is to obtain therapeutic temperatures at the tumour periphery and adequate deep heating when using a single applicator. The use of multiple applicators has therefore been investigated in order to improve the power distribution. Anatomical topography often permits the application of two tilted applicators, e.g. in the head and neck area, on extremities and on large protruding tumours. Theoretical calculations of the absorbed power distribution from such an applicator configuration were performed in a homogeneous muscle equivalent medium. The power distribution from two conventional radiative apertures (TE_{10}) was studied at different frequencies, aperture sizes, tilting angles and non-coherent or coherent fields in phase. The use of two applicators, excited coherently in phase at the lower microwave or upper radiofrequency band, can considerably improve the absorbed power distribution. Both depth penetration and lateral power distribution are superior when compared to those of a single applicator or two applicators excited non-coherently.

INTRODUCTION

The effectiveness of hyperthermia treatment of malignant tumours, either alone or in combination with radiation therapy, is strongly dependent on the temperature distribution attained in the treatment volume^{1,2,3}. Local hyperthermia treatment of superficial tumours is often based on external microwave heating by using radiative apertures working at the ISM-frequencies 2450 MHz, 915 MHz or 434 MHz^{4,5,6,7}. For these frequencies, the absorbed power decreases approximately exponentially with a penetration depth of a few cm in muscle-equivalent tissues. Besides, most applicators have a maximum power density at the centre of the aperture⁸.

Considerable temperature heterogeneity often occurs in the tumour volume. The major problem is to obtain therapeutic temperatures at the tumour periphery and adequate deep heating^{4,9,10}. This is to be expected when heating with a single applicator, whereby the largest specific absorption rate is at the centre of the lesion. This is the part of a solid tumour that requires the least absorbed power to attain a specific temperature rise, since the core of solid tumours generally has a lower perfusion than the viable periphery¹¹. In addition, according to biological studies, the centre of a solid tumour is also the most heat-sensitive part, as a result of poor nutrition and a resulting low pH-value¹².

Even if the tumour is heated homogeneously, there might be a temperature gradient at the periphery of the tumour due to heat conduction and differences in blood flow between the tumour and the surrounding normal tissue¹³. It would thus be better to heat the tumour preferentially at its edges.

The use of multiple applicators might improve the power distribution both laterally and at depth. Methods based on constructive interference between the fields from multiple

radiative applicators (annular phased array)¹⁴, a coaxial TEM-applicator¹⁵ and multiple inductive applicators¹⁶, all working in the radiofrequency range, have previously been described for regional focused deep-heating.

A numerical analysis of three-dimensional power distributions in a homogeneous muscle-equivalent medium has been performed to test if constructive interference with conventional applicators, working in the lower microwave or upper radiofrequency range, could be useful for improving power-deposition patterns in superficial tumours. The upper ISM-frequencies (2450 MHz and 915 MHz) are not suitable due to the limited penetration depth and the short wave-length in tissues with high water content. When interference techniques are used, long wave-lengths are desirable in order to minimize the phaseshift along a typical distance in the tissue volume studied. There is, however, also a lower frequency limit where radiative apertures of appropriate sizes can be used in actual practice. The suitable frequency range is thus from about 150 MHz up to about 400 MHz.

The mathematical theory has been based on the "Shelkunoff equivalent current approach"¹⁷ where the aperture fields are replaced by electric and magnetic surface currents. This theory has also been used by Turner and Kumar¹⁸ for calculation of absorbed power distributions in muscle tissue on the central axis for different apertures. Even though simplified tissue geometries and only homogeneous media are studied, the theoretical calculations give valuable information on the absorbed power distributions from different applicator configurations.

METHODS

A. Physical definitions

The aperture of the applicator is assumed to be in direct contact with a conducting plane perpendicular to the applicator surface. The electromagnetic fields in the aperture plane are regarded as sources for the exterior fields. The electric and magnetic fields on the closed applicator surface are replaced with electric and fictitious magnetic currents according to the field equivalence theorem¹⁹. The complex magnetic, $\vec{A}$, and electric, $\vec{F}$, vector potentials resulting from the electric, $\vec{J}_{se}$ (Am^{-1}), and magnetic, $\vec{J}_{sm}$ (Vm^{-1}), surface current densities, are given by the surface integrals¹⁹:

$$\vec{A} = \int_{s'} \frac{\mu \vec{J}_{se} e^{-\gamma r}}{4\pi R} ds' \quad (\text{Wb m}^{-1}) \quad (1)$$

$$\vec{F} = \int_{s'} \frac{\epsilon^* \vec{J}_{sm} e^{-\gamma r}}{4\pi R} ds' \quad (\text{C m}^{-1}) \quad (2)$$

where:

$\mu = \mu_r \mu_0$ = permeability of the medium ($\text{VsA}^{-1}\text{m}^{-1}$)

μ_r = relative permeability

$\mu_0 = 4\pi \cdot 10^{-7} \text{ VsA}^{-1}\text{m}^{-1}$ = permeability of free space

$\epsilon^* = \epsilon_0 (\epsilon'_r - j\epsilon''_r) = \epsilon_0 (\epsilon'_r - \frac{j\sigma}{\omega\epsilon_0})$ = permittivity of the medium ($\text{AsV}^{-1}\text{m}^{-1}$)

$\epsilon_0 = 8.854 \cdot 10^{-12} \text{ AsV}^{-1}\text{m}^{-1}$ = permittivity of free space

ϵ'_r = relative permittivity

σ = conductivity of the medium (Sm^{-1})

ω = angular frequency of the electromagnetic field (s^{-1})

The propagation constant, γ , is defined as²⁰:

$$\begin{aligned}\gamma &= \alpha + j\beta = \{ j\omega\mu (j\omega\epsilon'_r\epsilon_o + \sigma) \}^{\frac{1}{2}} = \\ &= j\omega \{ \mu\epsilon_o (\epsilon'_r - \frac{j\sigma}{\omega\epsilon_o}) \}^{\frac{1}{2}} \quad (\text{m}^{-1})\end{aligned}\quad (3)$$

All vector fields are in the complex time harmonic form. With the applicator placed in a coordinate system as defined in Fig. 1, and polarized in the y-direction, the boundary conditions for the aperture result in¹⁹:

$$\vec{J}_{sm} = -\vec{a}_z \times \vec{E}^i = E^i \vec{a}_x \quad (\text{V m}^{-1}) \quad (4)$$

and

$$\vec{J}_{se} = \vec{a}_z \times \vec{H}^i = -\frac{E^i}{\eta} \vec{a}_y \quad (\text{A m}^{-1}) \quad (5)$$

where

E^i and H^i are the incident tangential electric and magnetic fields in the aperture at $z=0$,

η is the wave impedance of the applicator,

and $\vec{a}_x$, $\vec{a}_y$ and $\vec{a}_z$ are unit vectors.

When E^i and H^i are known, the vector potentials $\vec{A}$ and $\vec{F}$ can theoretically be calculated from equations 1-5 and thereby the electric and magnetic fields in the medium¹⁹.

B. Numerical method

A mathematical solution method, with numerical integration, can be used if the aperture is simulated with an array of point-source dipoles, placed at the aperture surface at equi-distant points (Fig. 2), simulating the original radiation surface. The magnetic and electric vector potentials from the small difference current-elements with the electric, J_e (Am), and magnetic, J_m (Vm), currents are:

$$d\vec{A} = \frac{\mu \vec{J}_e e^{-\gamma r}}{4\pi r} \quad (\text{Wb m}^{-1}) \quad (6)$$

and

$$d\vec{F} = \frac{\epsilon^* \vec{J}_m e^{-\gamma r}}{4\pi r} \quad (\text{C m}^{-1}) \quad (7)$$

where r is the distance from the source.

The magnetic field resulting from the magnetic vector potential is¹⁹:

$$d\vec{H}_e = \frac{1}{\mu} \vec{\nabla} \times d\vec{A} \quad (\text{A m}^{-1}) \quad (8)$$

and the induced electric field is obtained from Maxwell's equations:

$$d\vec{E}_e = \frac{1}{j\omega\epsilon^*} \vec{\nabla} \times d\vec{H}_e \quad (\text{V m}^{-1}) \quad (9)$$

Using the symmetric Maxwell's equations¹⁹, the corresponding fields from the electric vector potential are:

$$d\vec{E}_m = - \frac{1}{\epsilon^*} \vec{\nabla} \times d\vec{F} \quad (\text{V m}^{-1}) \quad (10)$$

and

$$d\vec{H}_m = - \frac{1}{j\omega\mu} \vec{\nabla} \times d\vec{E}_m \quad (\text{A m}^{-1}) \quad (11)$$

Only the electric fields need be considered, however, since $\mu = \mu_0$ for biological tissues. The solutions for the electric fields from the dipole sources are in spherical coordinates, defined as in Fig. 3¹⁸:

$$\vec{dE}_{e\phi} = \frac{-J_e \cos\phi e^{-\gamma r}}{4\pi j\omega\epsilon^*} \left(\frac{1}{r^3} + \frac{\gamma}{r^2} + \frac{\gamma^2}{r} \right) \vec{a}_\phi \quad (12)$$

$$\vec{dE}_{e\theta} = \frac{-J_e \cos\theta \sin\phi e^{-\gamma r}}{4\pi j\omega\epsilon^*} \left(\frac{1}{r^3} + \frac{\gamma}{r^2} + \frac{\gamma^2}{r} \right) \vec{a}_\theta \quad (13)$$

$$\vec{dE}_r = \frac{J_e \sin\theta \sin\phi e^{-\gamma r}}{2\pi j\omega\epsilon^*} \left(\frac{1}{r^3} + \frac{\gamma}{r^2} \right) \vec{a}_r \quad (14)$$

$$\vec{dE}_{m\theta} = \frac{-J_m \sin\phi e^{-\gamma r}}{4\pi} \left(\frac{1}{r^2} + \frac{\gamma}{r} \right) \vec{a}_\theta \quad (15)$$

$$\vec{dE}_{m\phi} = \frac{-J_m \cos\theta \cos\phi e^{-\gamma r}}{4\pi} \left(\frac{1}{r^2} + \frac{\gamma}{r} \right) \vec{a}_\phi \quad (16)$$

Equations 12 to 14 are the regular electric field expressions for an electric dipole source¹⁹. By vectorially summing the dE-terms for all dipoles, the total electric field strength can be calculated at any point, $P=(x_p, y_p, z_p)$, in the medium.

As shown by Turner and Kumar¹⁸, the $\vec{E}_e$ -fields contribute little to the power deposition in tissue at frequencies above 1 MHz. Only frequencies above about 100 MHz are of interest in this work, and therefore these fields will be neglected in the following.

The $\vec{E}_m$ -terms, when vectorially added, have no component in the x-direction. The definitions of angles are therefore transformed according to Fig. 4. The former $\vec{E}_{m\theta}$ - and $\vec{E}_{m\phi}$ -terms compose in this new coordinate system only one term, being

$$\vec{dE} = \frac{J_m}{4\pi} \sin\theta' \left(\frac{1}{r^2} + \frac{\gamma}{r} \right) e^{-\gamma r} \vec{a}_\phi, \quad (17)$$

According to Equation 4, the magnetic surface current density is equal to the incident electric field strength at the aperture

surface. One of the most frequently used applicators in clinical hyperthermia treatment of superficial tumours is probably the waveguide applicator excited in the fundamental TE₁₀-mode. It is easy to construct and has a well-known inherent field pattern. This applicator type is used in all of the following calculations, though any other radiative aperture with a known field configuration could be used. For a TE₁₀-waveguide applicator, the electric field strength is constant in the y-direction, but varies in the x-direction as:

$$E_{yc}^i(x,y,0) = E_{yc}^i \sin\left(\frac{\pi x}{a}\right) \quad \begin{matrix} 0 < x < a \\ 0 < y < b \end{matrix} \quad (18)$$

E_{yc}^i is the field at the centre of the aperture and a and b are the dimensions of the aperture. The electric field at a point of a distance r from the dipole source situated at (x,y,0) is thus:

$$dE = C \sin\left(\frac{\pi x}{a}\right) \sin\theta' \left(\frac{1}{r^2} + \frac{\alpha}{r} + \frac{j\beta}{r} \right) e^{-\alpha r} e^{-j\beta r} \vec{a}_\phi, \quad (19)$$

where C is a constant.

The propagation constant is $\gamma = \alpha + j\beta$, with the amplitude attenuation constant:

$$\alpha = \omega \left(\frac{\mu\epsilon_0\epsilon_r'}{2} \right)^{\frac{1}{2}} \left\{ \left(1 + \left(\frac{\sigma}{\omega\epsilon_0\epsilon_r'} \right)^2 \right)^{\frac{1}{2}} - 1 \right\}^{\frac{1}{2}} \quad (m^{-1}) \quad (20)$$

and the phase constant:

$$\beta = \omega \left(\frac{\mu\epsilon_0\epsilon_r'}{2} \right)^{\frac{1}{2}} \left\{ \left(1 + \left(\frac{\sigma}{\omega\epsilon_0\epsilon_r'} \right)^2 \right)^{\frac{1}{2}} + 1 \right\}^{\frac{1}{2}} \quad (m^{-1}) \quad (21)$$

The amplitude attenuation constant is further

$$\alpha = 1/d_s \quad (m^{-1}) \quad (22)$$

where d_s is the penetration depth, the "skin depth", i.e. the

depth at which the amplitude of the E-field has decreased to 1/e (37%) of its value at the reference depth. The phase constant is related to the wavelength in the medium, λ_m ,

$$\beta = 2\pi/\lambda_m \quad (m^{-1}) \quad (23)$$

With knowledge of d_s and λ_m , the electric field from a dipole can thus be calculated in any point of the medium by using Equation 19. The real-time form of the field of the oscillating dipole element with the frequency $f = \omega/2\pi$ becomes:

$$\begin{aligned} dE_{Re} &= \text{Re} \{ dE e^{j\omega t} \} = \\ &= C \cdot \sin\left(\frac{\pi x}{a}\right) \cdot \sin \theta' \left\{ \left(\frac{1}{r^2} + \frac{\alpha}{r}\right) \cos(\omega t - \beta r) - \frac{\beta}{r} \sin(\omega t - \beta r) \right\} e^{-\alpha r} \end{aligned} \quad (24)$$

with the $\vec{E}$ -vector oscillating in the $\vec{a}_\phi$ -direction.

For each point in the medium, the E-fields from the dipoles are vectorially added, and the peak value of the length of the total $\vec{E}$ -vector, $\vec{E}$, can thus be calculated.

The power deposited per unit volume of the medium is:

$$P_{abs} = \frac{1}{2} \sigma |\vec{E}|^2 \quad (W \ m^{-3}) \quad (25)$$

which is related to the specific absorption rate, "SAR":

$$SAR = P_{abs}/\rho \quad (W \ kg^{-1}) \quad (26)$$

where ρ is the density of the medium.

Assuming constant σ and ρ , the square of the length of the resulting E-vector is thus proportional to SAR.

C. Dual applicators

The power distribution from two applicators, arranged as shown in Fig. 5, has been studied. The applicators can be tilted at arbitrary angles, δ . The power distribution from the applicators can be calculated either without coherence criteria between them, or coherently with a specific phase relation, by adding a phase angle, φ . The argument ($\omega t - \beta r$) in Equation 24 is thus changed to ($\omega t - \beta r + \varphi$) for the dipoles of one of the applicators.

D. Computer program

A computer program coded in FORTRAN was written for calculation of the absorbed power density distribution from one or two TE₁₀-applicators according to Equations 24 and 25.

Input data are:

- applicator size ($a \times b$)
- distance between the dipole sources (d_d),
- phase relation between the applicators (φ),
- tilting angle (δ),
- penetration depth (d_s),
- wave-length in the medium (λ_m), and
- co-ordinates for a point at which the absorbed power is normalized (x_n, y_n, z_n).

The normalization point is always situated at the central axis of the applicator and 5 mm in front of the aperture plane, if not otherwise specifically noted.

The density of the dipole sources needed is dependent on the z-co-ordinate for the calculation point, the penetration depth and the wave-length in the medium. The distance between the sources, d_d , usually 2 or 5 mm, has been chosen as great as possible to

minimize computer run-time, but so small that a more dense array of dipoles does not significantly change the power distribution pattern.

The permittivity and conductivity of muscle tissue according to Johnson and Guy²¹ have been used. These are summarized in Table I for the frequencies studied.

RESULTS AND DISCUSSION

A. Single applicator

To test the performance of the computer program, the depth penetration in muscle tissue was calculated for a fixed frequency of 434 MHz and various aperture sizes (Fig. 6), and for a fixed applicator size of $10 \times 10 \text{ cm}^2$ at different frequencies (Fig. 7). The results of Turner and Kumar¹⁸ are confirmed: The penetration characteristics are strongly dependent on the aperture size in relation to the wave-length in the tissue²². This is a result of the spreading of the beam when the aperture is small compared to the wave-length²³. The superiority of 915 MHz over 2450 MHz for depth penetration is clearly shown. For 915 MHz, the penetration depth for a $10 \times 10 \text{ cm}^2$ aperture is very close to that of a plane wave. By lowering the frequency, little is gained in penetration depth for the same aperture size. Even at 100 MHz, the penetration for a $10 \times 10 \text{ cm}^2$ aperture is less than for a plane wave at 434 MHz.

The actual heat distribution as a function of the depth in the tissue can to some extent be modified by controlling the surface temperature, with e.g. a water bolus or an air jet-stream^{4,5,6,7,10}. The heating pattern parallel to the applicator surface, however, is mainly governed by the characteristics of the applicator.

The power distribution parallel to the aperture surface from a $10 \times 10 \text{ cm}^2$ TE₁₀-waveguide applicator at 434 MHz and at different depths, z , is shown in Fig. 8 for the y -direction and in Fig. 9 for the x -direction. The absorbed power along the direction of the incident electric field (Fig. 8) is rather uniform due to the constant field strength in this direction. The homogeneity becomes poorer with increasing depth due to the spreading of the beam.

In the direction normal to the applicator electric field (Fig. 9) the power distribution has a marked peak at the center of the aperture due to the variation of the E^i -field in the x-direction. The spreading of the beam with increasing depth tends to somewhat flatten out the power distribution.

The theoretical calculations were also compared to earlier experimental phantom measurements on a $9.4 \times 9.4 \text{ cm}^2$ applicator used in our clinical 915 MHz hyperthermia system⁷. The dielectric characteristics for the specific muscle-equivalent phantom used are $\epsilon^* = \epsilon_0(\epsilon'_r - j\epsilon''_r) = \epsilon_0(54 - j28)$, and thus: $\sigma = \epsilon_0\epsilon''_r \omega = 1.43 \text{ Sm}^{-1}$, resulting in $d_s = 28 \text{ mm}$ and $\lambda_m = 43 \text{ mm}$ for 915 MHz (Equations 20 - 23), which are in good agreement with the values given by Johnson and Guy²¹ (Table I). The results are shown in Fig. 10 and Fig. 11. The theoretical data agree well with the experimental values.

It is evident that the physical size of the aperture must be much larger than the extensions of the treatment area, at least in the x-direction. Large aperture sizes are, however, difficult to apply in clinical hyperthermia treatments, especially in the head and neck area, on extremities and on large protruding tumours. Besides, even with a large aperture, the tumour will be heated preferentially at its central areas.

B. Dual applicators

At the anatomical locations mentioned it would be possible to use two applicators arranged as shown in Fig. 5. Calculations have been made for two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators with different tilting angles, δ , and for different frequencies, with or without phase relations. The practical lower frequency limit at these aperture sizes is about 200 MHz. For example, a water-filled ($\epsilon'_r \approx 78$) 10 cm wide applicator (cut-off wave-length: 177 cm) would be possible.

The absorbed power distribution was normalized at a point on the

central axis of one of the applicators, 5 mm in front of the aperture, and was calculated at points in a plane array ($y=50$ mm) with 5 mm spacing. From these data, iso-absorbed power distribution charts were drawn.

Fig. 12 and Fig. 13 show the power distributions for a tilting angle of 45° , i.e. the central axes of the applicators are perpendicular. Calculations are shown both for coherent radiation with a phase angle, $\varphi=0^\circ$, and for non-coherent radiation at 434 MHz and 200 MHz.

When there is no phase relation between the applicators, the beams from each applicator are clearly distinguished as two separate lobes. The power distribution is the sum of the contributions from each applicator. There is hardly any difference in the absorbed power-distribution patterns between 200 MHz and 434 MHz, since the penetration characteristics are almost identical for the two frequencies, with a 10×10 cm² aperture according to Fig. 2.

When the applicators are excited coherently in phase, the absorbed power patterns are changed considerably. The two separate lobes have diminished. For 200 MHz, the iso-absorbed power curves for 60% and lower values are almost straight lines parallel to the x-axis. The wave pattern for the corresponding curves at 434 MHz results in destructive interference at some locations, due to the shorter wave-length at this frequency.

When the fields are in coherence, the absolute value of the absorbed power at a point on the line $x=100$ mm is always twice the value compared to the case when the applicators are excited non-coherently. This is also approximately valid for the percentage data at 200 MHz (Fig. 12). At 434 MHz, with the applicators in coherence, however, the percentage data at this line are higher than twice the value of the non-coherent case. This is due to the fact that the distance between the

normalization points is close to $1.5 \lambda_m$, which means that the resulting E-vectors from each applicator are out of phase at these locations.

In Fig. 14 and Fig. 15 the tilting angle has been decreased to 30° . The power absorbed centrally between the applicators is decreased, but there is still a clear difference between the coherent and non-coherent cases. The resulting heat distribution is improved when heat conduction is taken into account, and if surface temperature regulation is applied. Besides, when two applicators in this configuration are used on a protruding tumour, the lesion is heated preferentially at its edges and with a better depth penetration than would be the case even with a large single aperture.

We must also consider the power distribution in the y-direction. The absorbed power in this direction at $x=100$ mm is shown in Fig. 16 for the dual applicator configuration, with a tilting angle of 45° . The homogeneity is impaired with increasing depth, z . Locations at large depths at mid-point between the applicators are also at large distances from each aperture surface, which, according to Fig. 8, leads to a loss in focusing of the beam.

To improve the power distribution in the y-direction, the height b of the applicator must obviously be increased. The data from two applicators, tilted 45° and each 10 cm wide, but with an aperture height of 175 mm, i.e. $2 \lambda_m$ at 434 MHz, are shown in Fig. 17. The larger aperture height results in a much improved power distribution in the direction parallel to the incident electric fields from the applicators. At 434 MHz, multiple lobes even lead to higher power values at off-centre locations.

C. Conclusion

The use of two conventional radiative apertures excited coherently in phase at the lower microwave or upper

radiofrequency band can considerably improve the absorbed power distribution in superficial tumours where anatomical topography permits the application of two tilted applicators. Both depth penetration and lateral power distribution are superior, when compared to those of a single applicator.

ACKNOWLEDGEMENT

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TABLE I. Properties of electromagnetic waves in muscle tissue (Ref. 21).

Frequency, f MHz	Relative permittivity, ϵ_r'	Conductivity, σ Sm^{-1}	Penetration depth, d mm	Wave-length, λ mm
2450	47	2.17	17	18
915	51	1.28	30	45
434	53	1.18	36	88
300	54	1.15	39	119
200	56.5	1.00	48	166
100	71.7	0.885	67	270

FIGURE CAPTIONS

- Fig. 1. The applicator location with the direction of the aperture fields, $\vec{E}^i$ and $\vec{H}^i$, and its equivalent magnetic, $\vec{J}_{sm}$, and electric, $\vec{J}_{se}$, surface current vectors.
- Fig. 2. The aperture with the point-source dipoles, simulating the original radiation surface. The total field in an arbitrary point, P, is the vectorial sum of the field contributions from all dipoles in that specific point.
- Fig. 3. Definition of the spherical coordinates for the field expressions in Equations 12-16.
- Fig. 4. Definition of the spherical coordinates for the field expression in Equation 17.
- Fig. 5. Dual applicator set-up.
- Fig. 6. Absorbed power distribution as a function of depth in a muscle-equivalent medium for 434 MHz and different applicator sizes (cm^2).
- Fig. 7. Absorbed power distribution as a function of depth in a muscle-equivalent medium for a $10 \times 10 \text{ cm}^2$ aperture at different frequencies (MHz).
- Fig. 8. Absorbed power distribution parallel to the aperture surface and parallel to the incident electric field at different depths for a $10 \times 10 \text{ cm}^2$ aperture at 434 MHz.
- Fig. 9. Absorbed power distribution parallel to the aperture surface and perpendicular to the incident electric field at different depths for a $10 \times 10 \text{ cm}^2$ aperture at 434 MHz.

Fig. 10. Absorbed power distribution (normalized at $z=2$ mm) as a function of depth for a 9.4×9.4 cm² aperture at 915 MHz (—: calculated curve; ●: experimental values).

Fig. 11. Absorbed power distribution (normalized at $z=2$ mm) parallel to the aperture surface for a 9.4×9.4 cm² aperture at 915 MHz (—: calculated curve; ●, ○: experimental values).

Fig. 12. Iso-absorbed-power distribution from two 10×10 cm² TE₁₀-applicators tilted 45° at 200 MHz with
a) coherent fields in phase
b) non-coherent fields.

Fig. 13. Iso-absorbed-power distribution from two 10×10 cm² TE₁₀-applicators tilted 45° at 434 MHz with
a) coherent fields in phase
b) non-coherent fields.

Fig. 14. Iso-absorbed-power distribution from two 10×10 cm² TE₁₀-applicators tilted 30° at 200 MHz with
a) coherent fields in phase
b) non-coherent fields.

Fig. 15. Iso-absorbed-power distribution from two 10×10 cm² TE₁₀-applicators tilted 30° at 434 MHz with
a) coherent fields in phase
b) non-coherent fields.

Fig. 16. Absorbed power distribution parallel to the incident electric field from two 10×10 cm² TE₁₀-applicators tilted 45° and excited in phase at 200 MHz (—) and at 434 MHz (---).

Fig. 17. Absorbed power distribution parallel to the incident

electric field from two $10 \times 17.5 \text{ cm}^2$ TE_{10} -applicators tilted 45° and excited in phase at 200 MHz (—) and at 434 MHz (---).

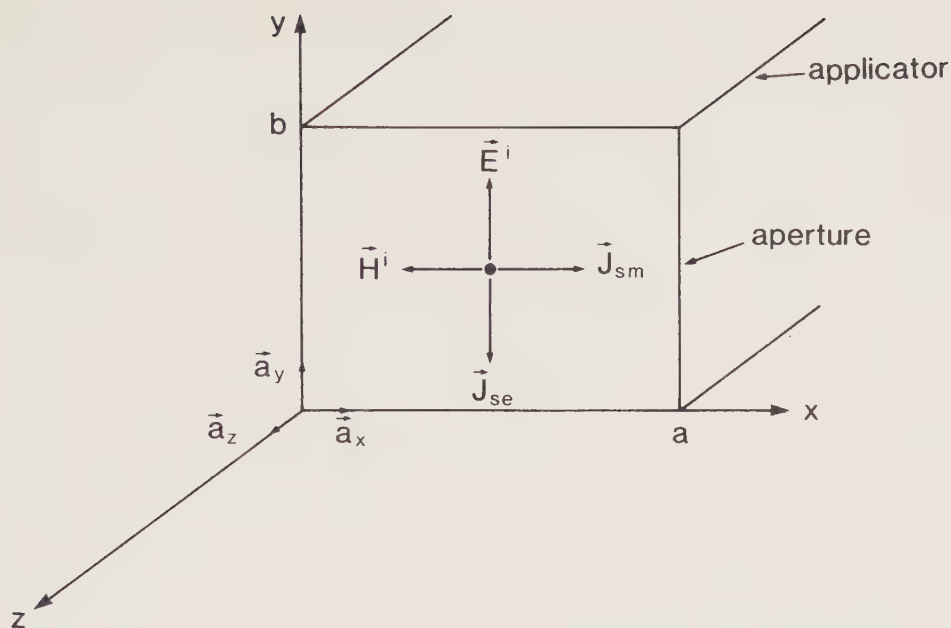


Fig. 1. The applicator location with the direction of the aperture fields, $\vec{E}^i$ and $\vec{H}^i$, and its equivalent magnetic, $\vec{J}_{sm}$, and electric, $\vec{J}_{se}$, surface current vectors.

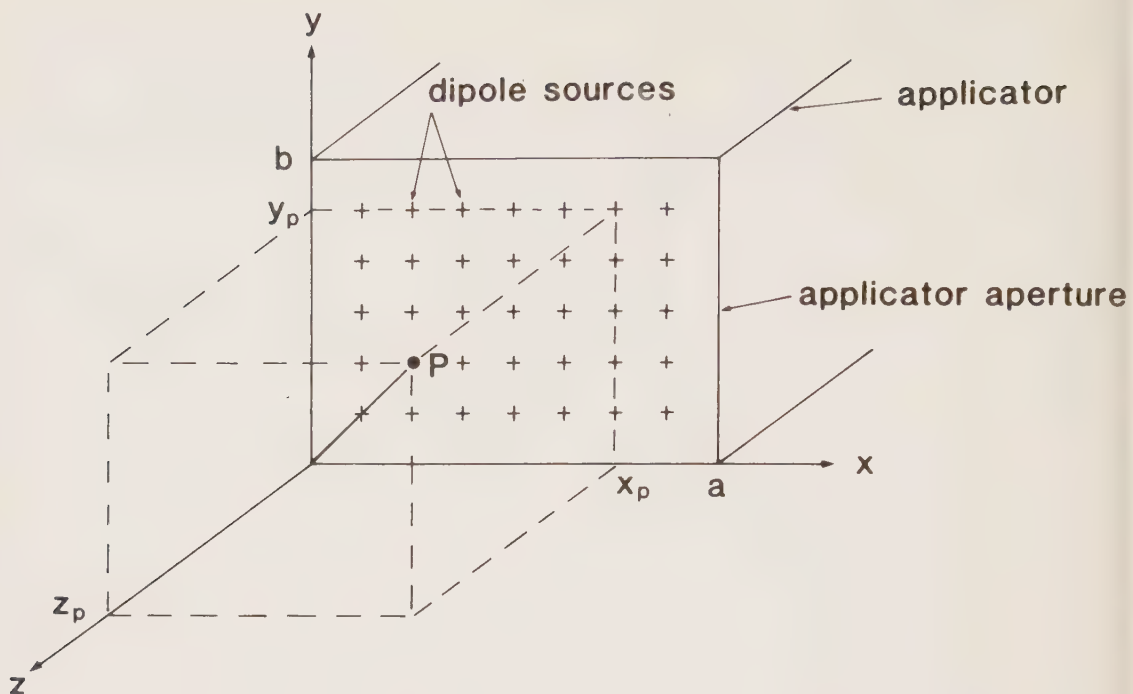


Fig. 2. The aperture with the point-source dipoles, simulating the original radiation surface. The total field in an arbitrary point, P , is the vectorial sum of the field contributions from all dipoles in that specific point.

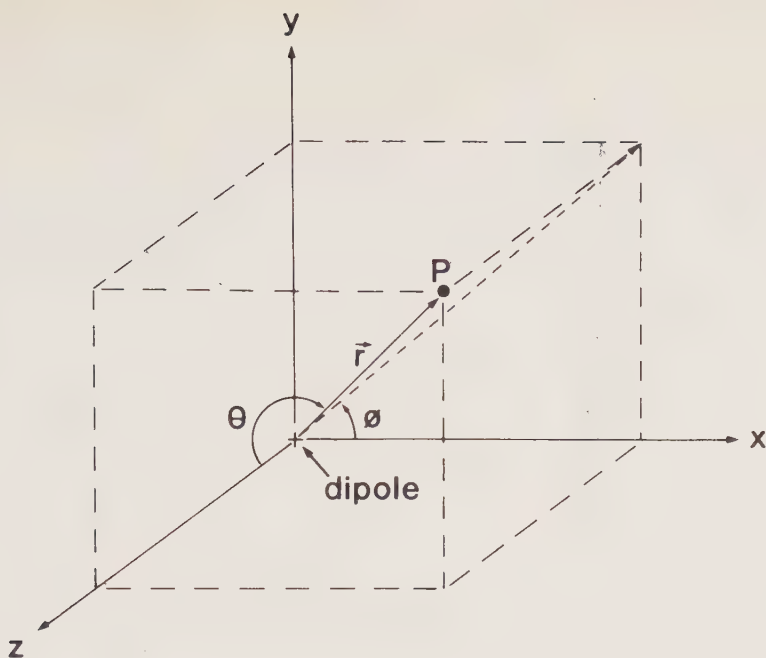


Fig. 3. Definition of the spherical coordinates for the field expressions in Equations 12-16.

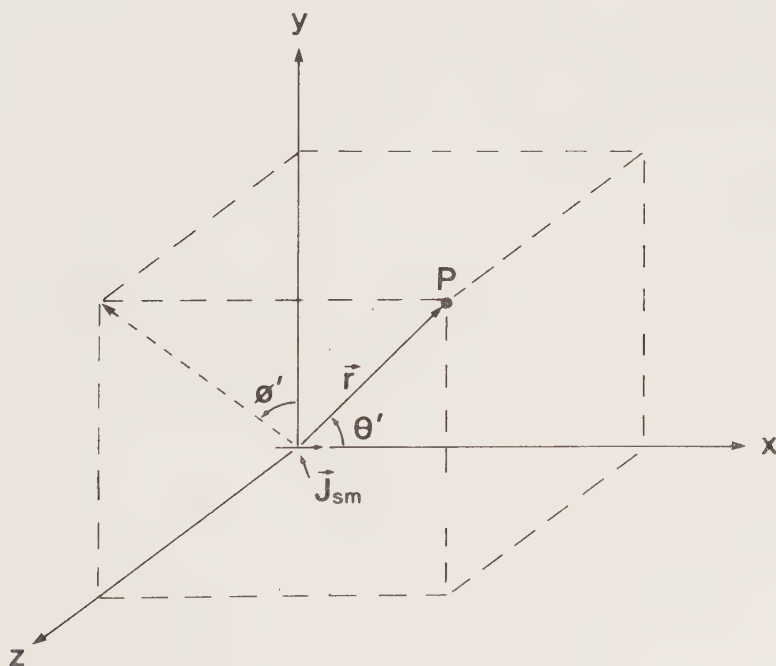


Fig. 4. Definition of the spherical coordinates for the field expression in Equation 17.

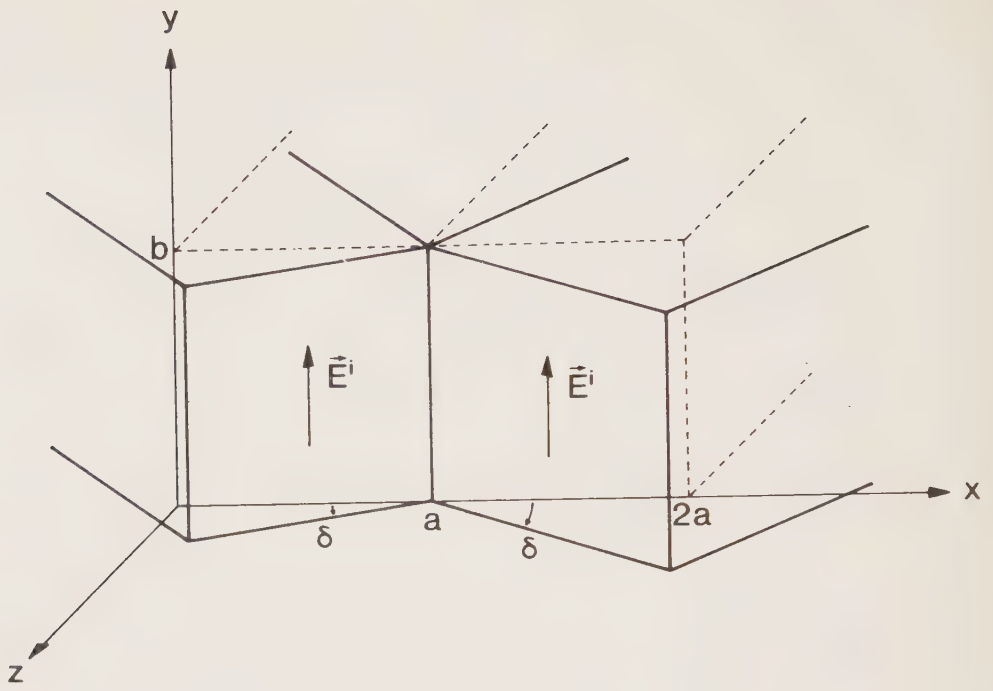


Fig. 5. Dual applicator set-up.

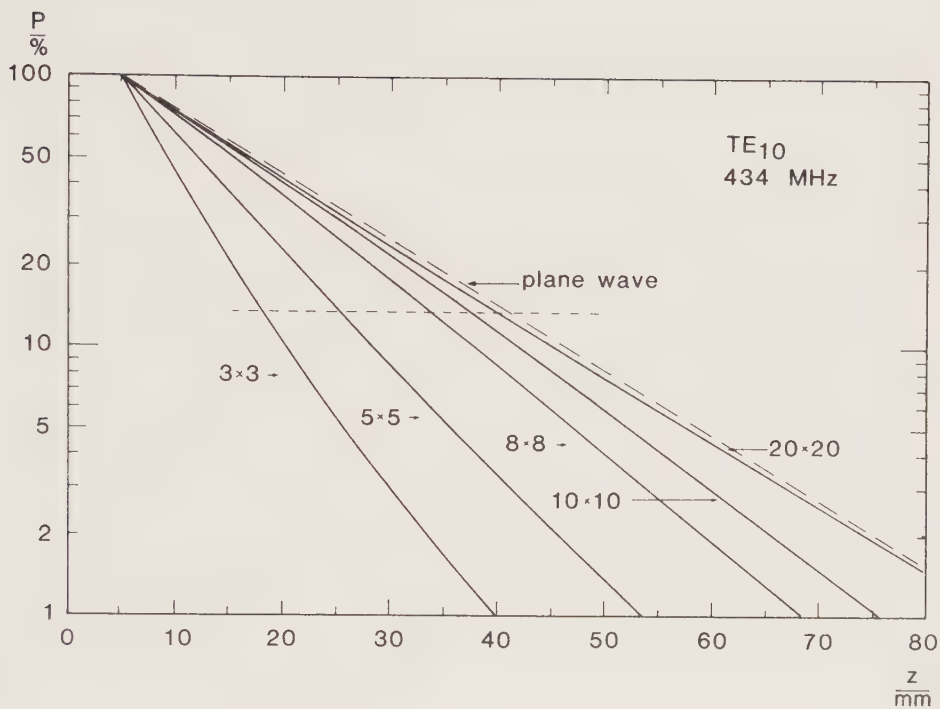


Fig. 6. Absorbed power distribution as a function of depth in a muscle-equivalent medium for 434 MHz and different applicator sizes (cm²).

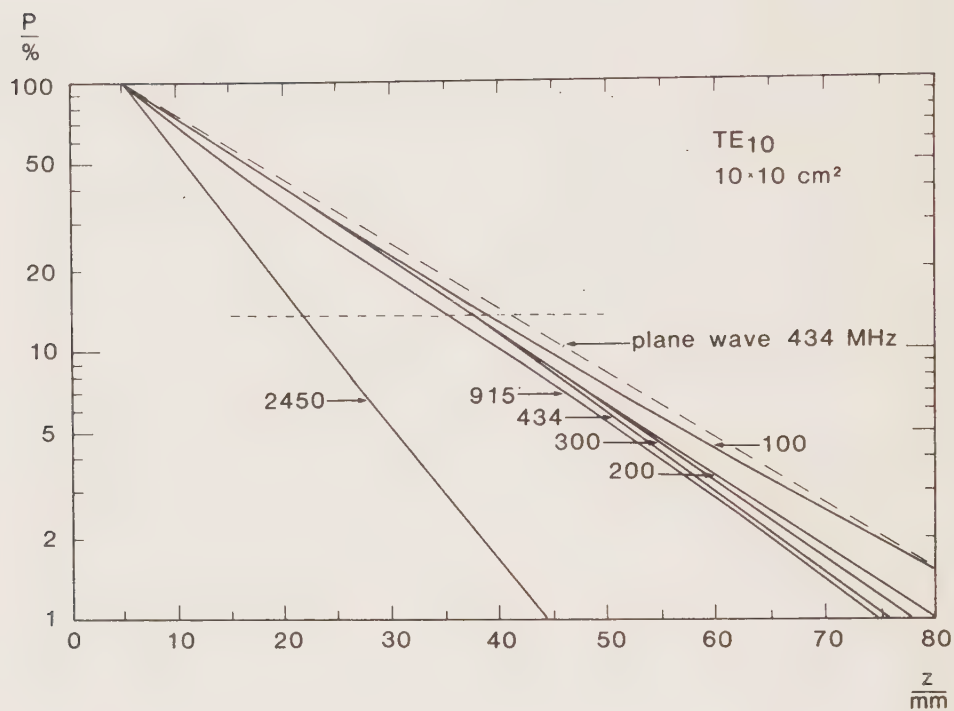


Fig. 7. Absorbed power distribution as a function of depth in a muscle-equivalent medium for a 10x10 cm² aperture at different frequencies (MHz).

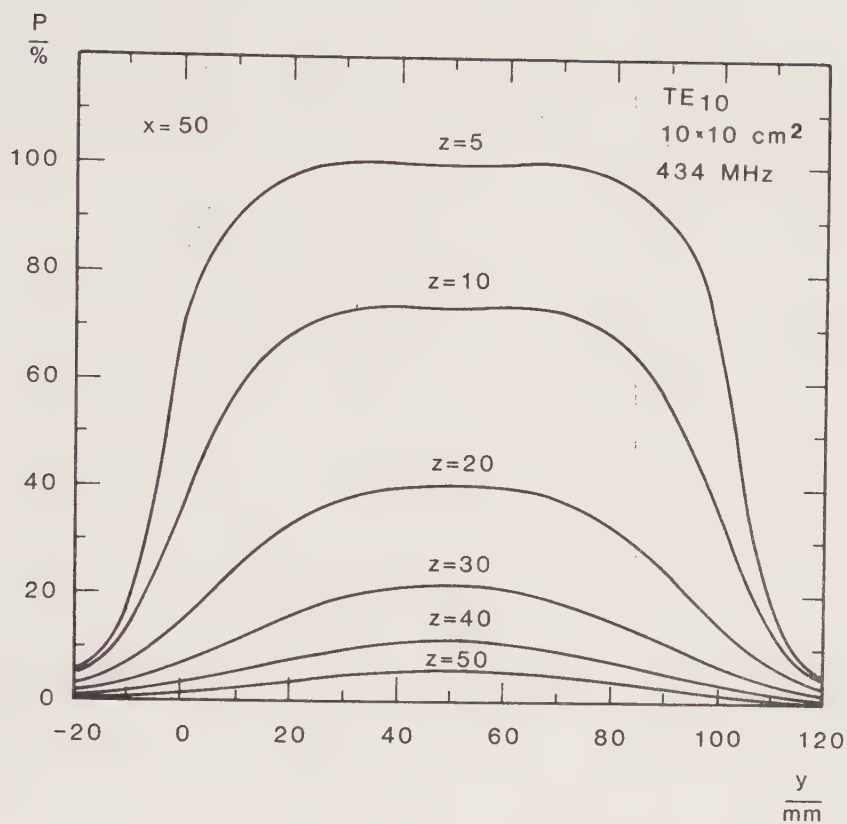


Fig. 8. Absorbed power distribution parallel to the aperture surface and parallel to the incident electric field at different depths for a $10 \times 10 \text{ cm}^2$ aperture at 434 MHz.

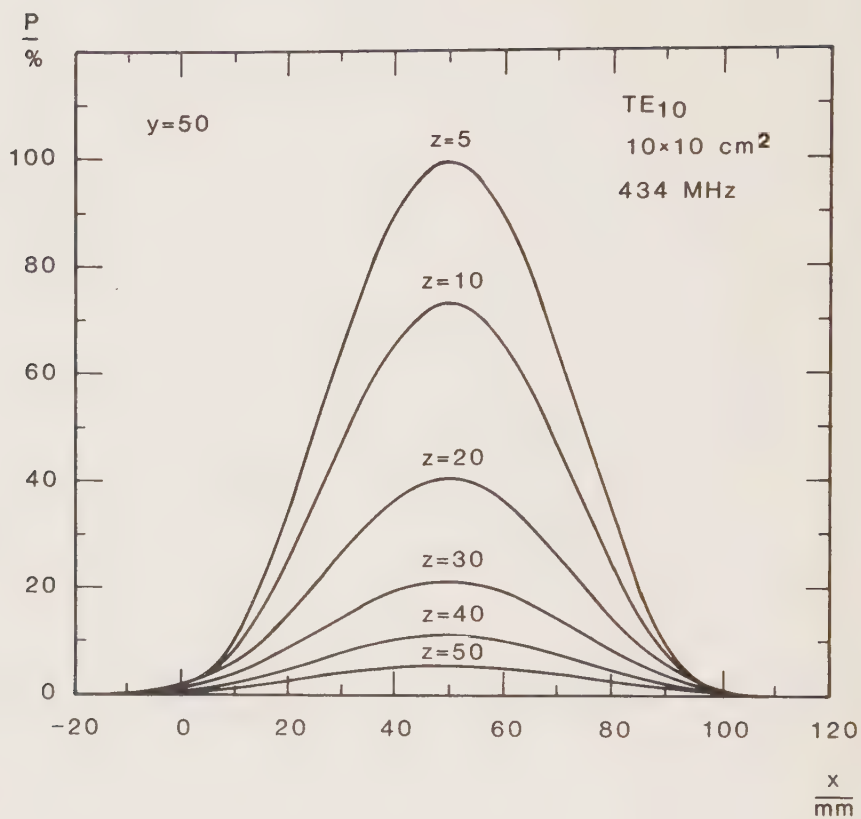


Fig. 9. Absorbed power distribution parallel to the aperture surface and perpendicular to the incident electric field at different depths for a 10×10 cm² aperture at 434 MHz.

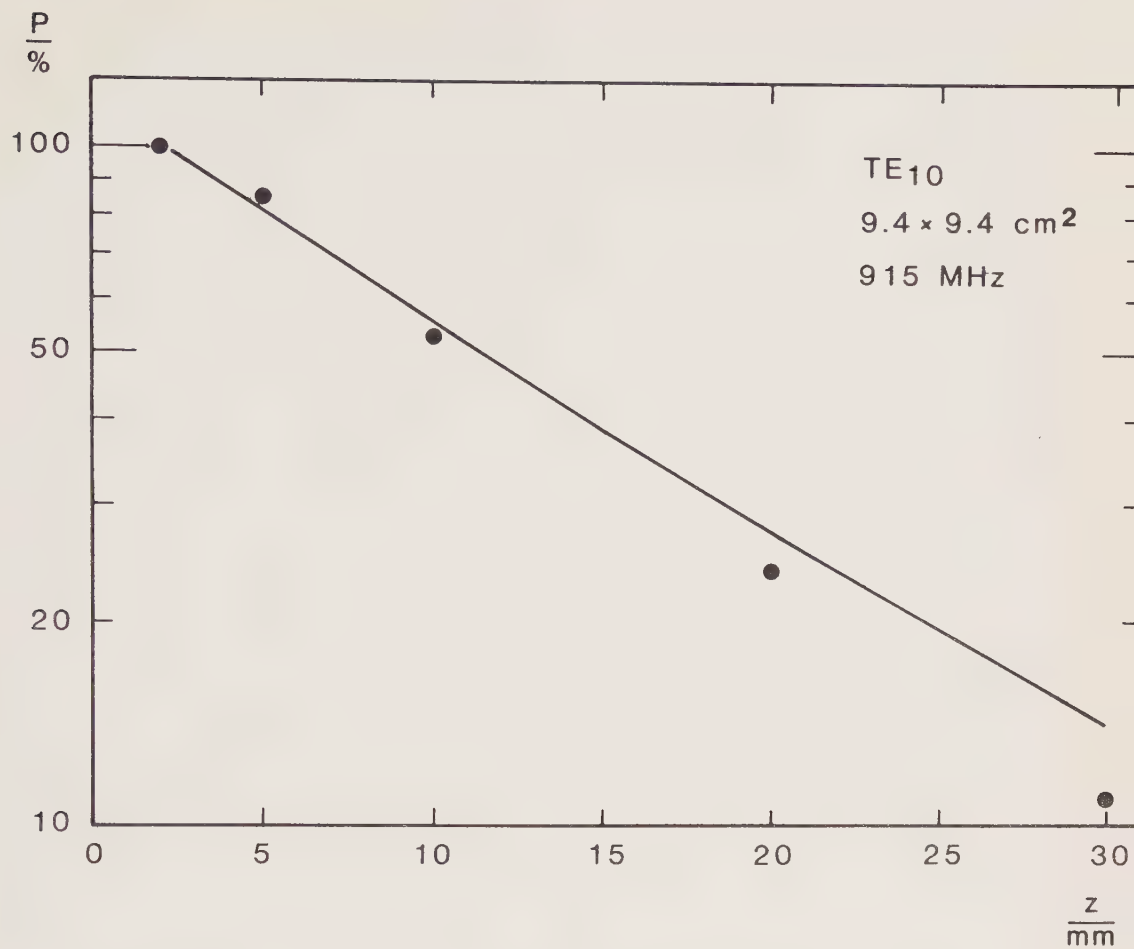


Fig. 10. Absorbed power distribution (normalized at $z=2$ mm) as a function of depth for a 9.4×9.4 cm² aperture at 915 MHz (—: calculated curve; •: experimental values).

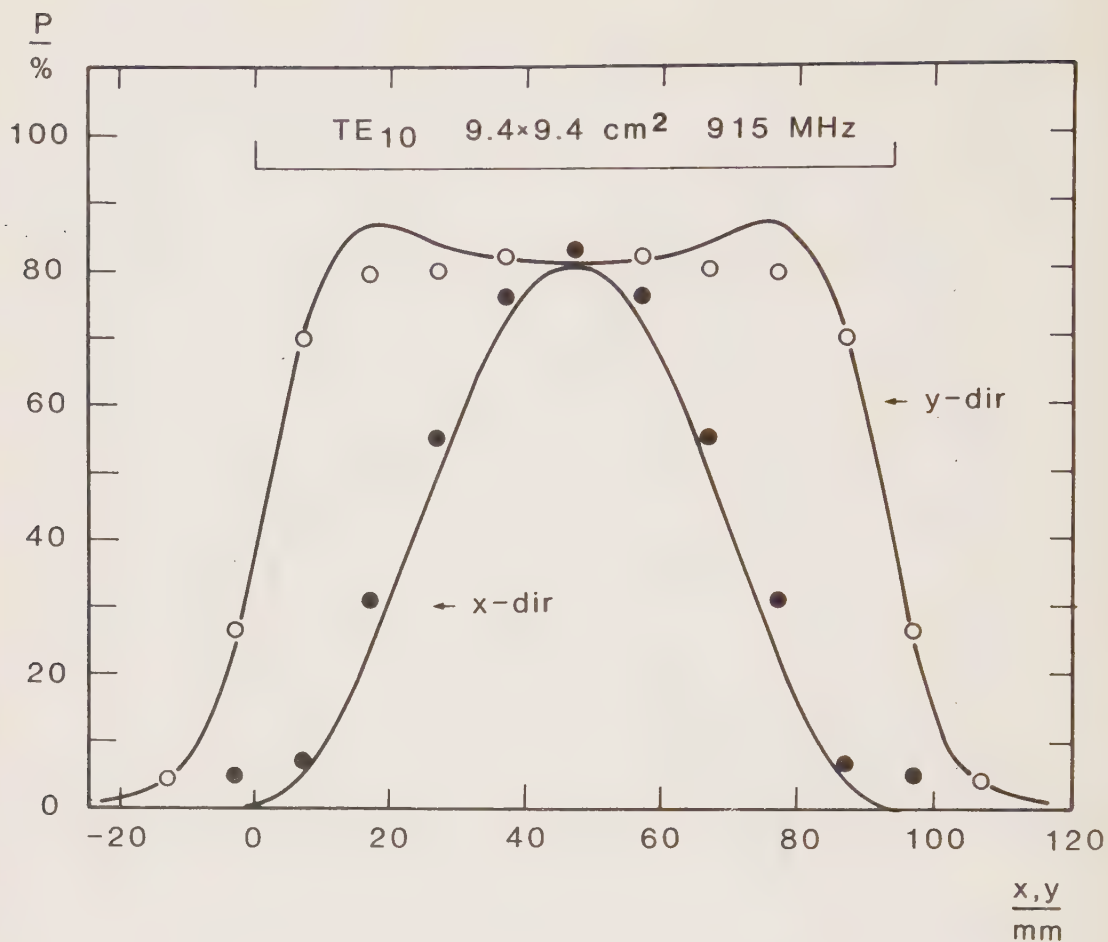


Fig. 11. Absorbed power distribution (normalized at $z=2$ mm) parallel to the aperture surface for a 9.4×9.4 cm² aperture at 915 MHz (—: calculated curve; ●, ○: experimental values).

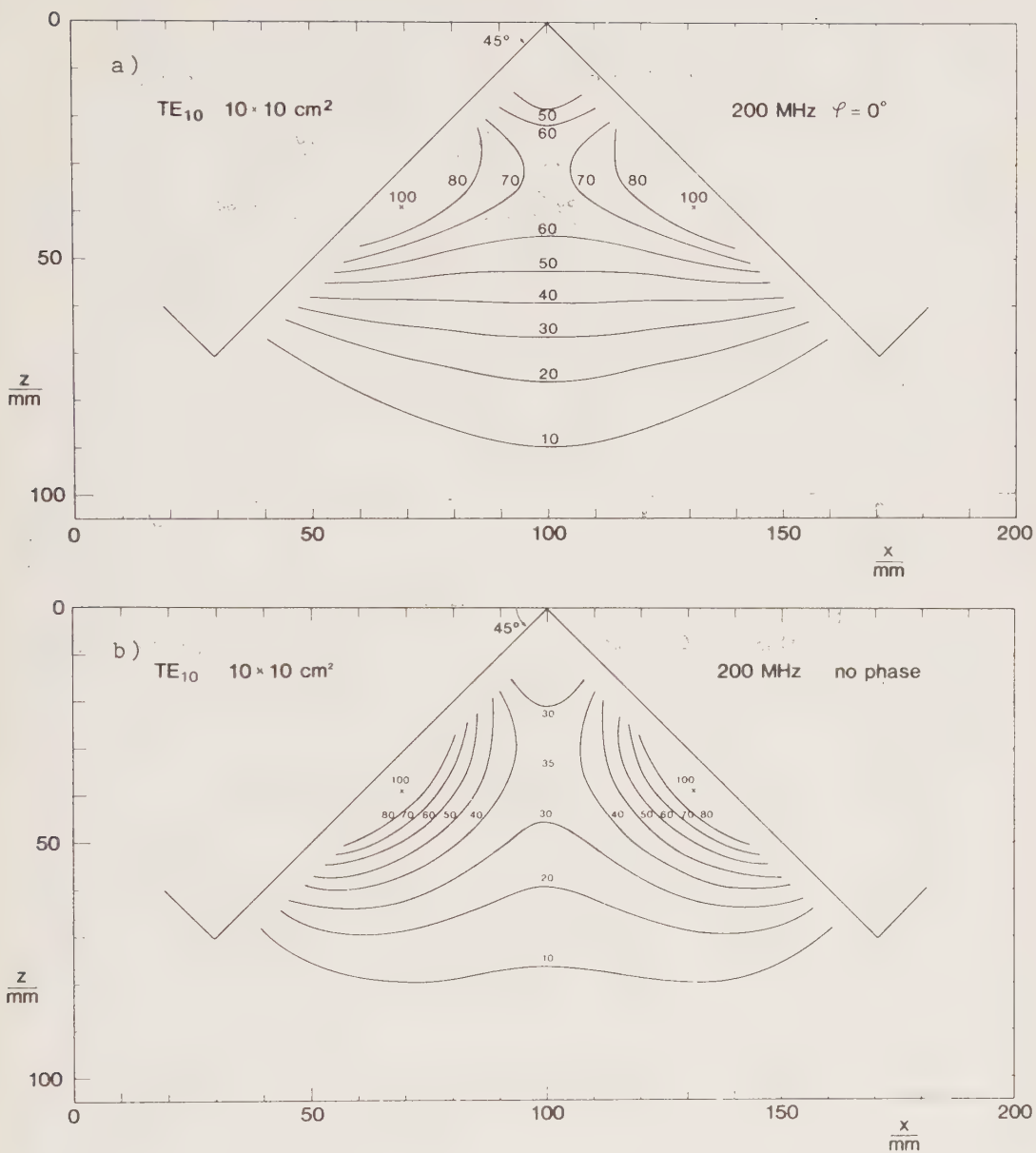


Fig. 12. Iso-absorbed-power distribution from two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators tilted 45° at 200 MHz with
a) coherent fields in phase
b) non-coherent fields.

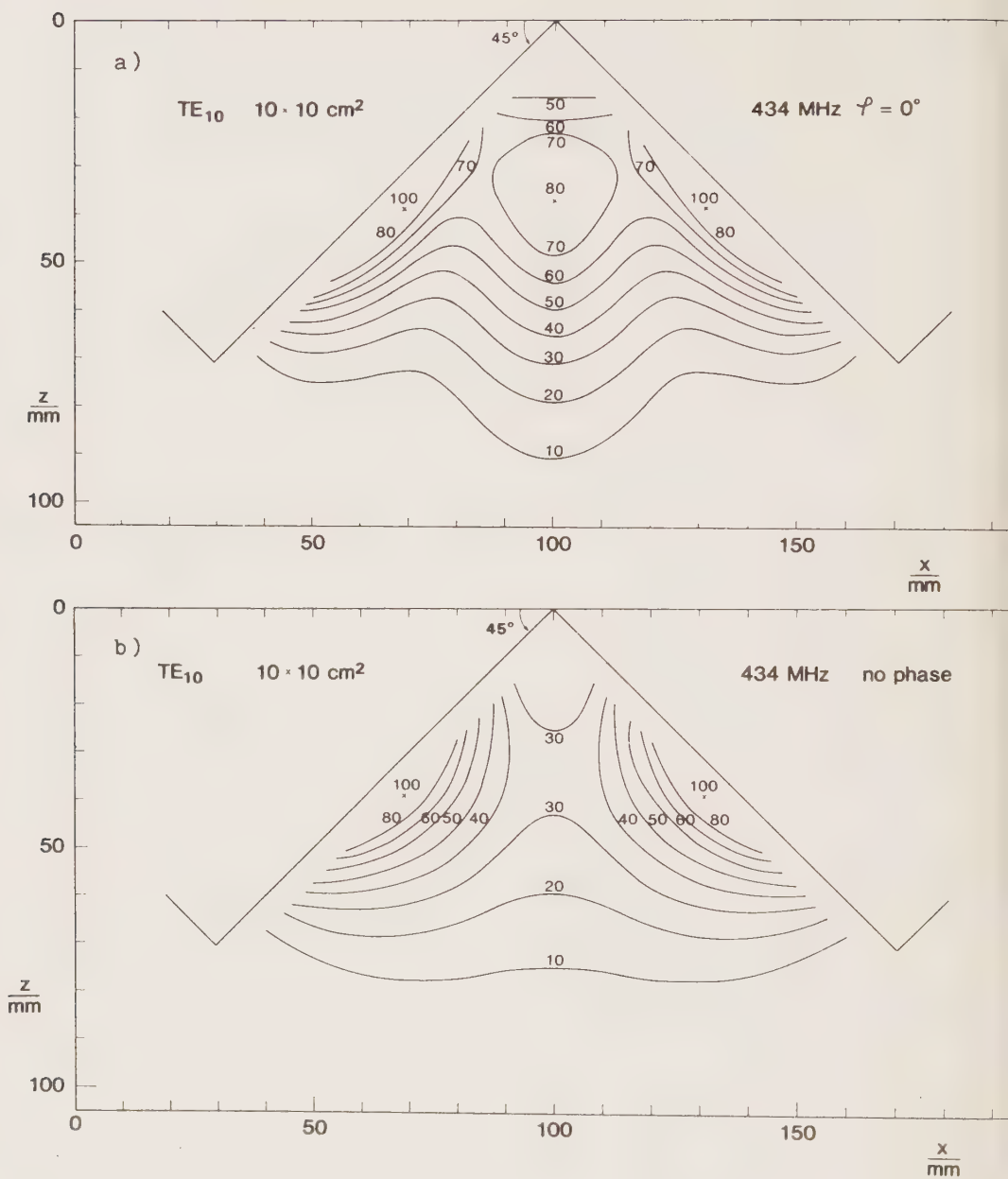


Fig. 13. Iso-absorbed-power distribution from two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators tilted 45° at 434 MHz with
a) coherent fields in phase
b) non-coherent fields.

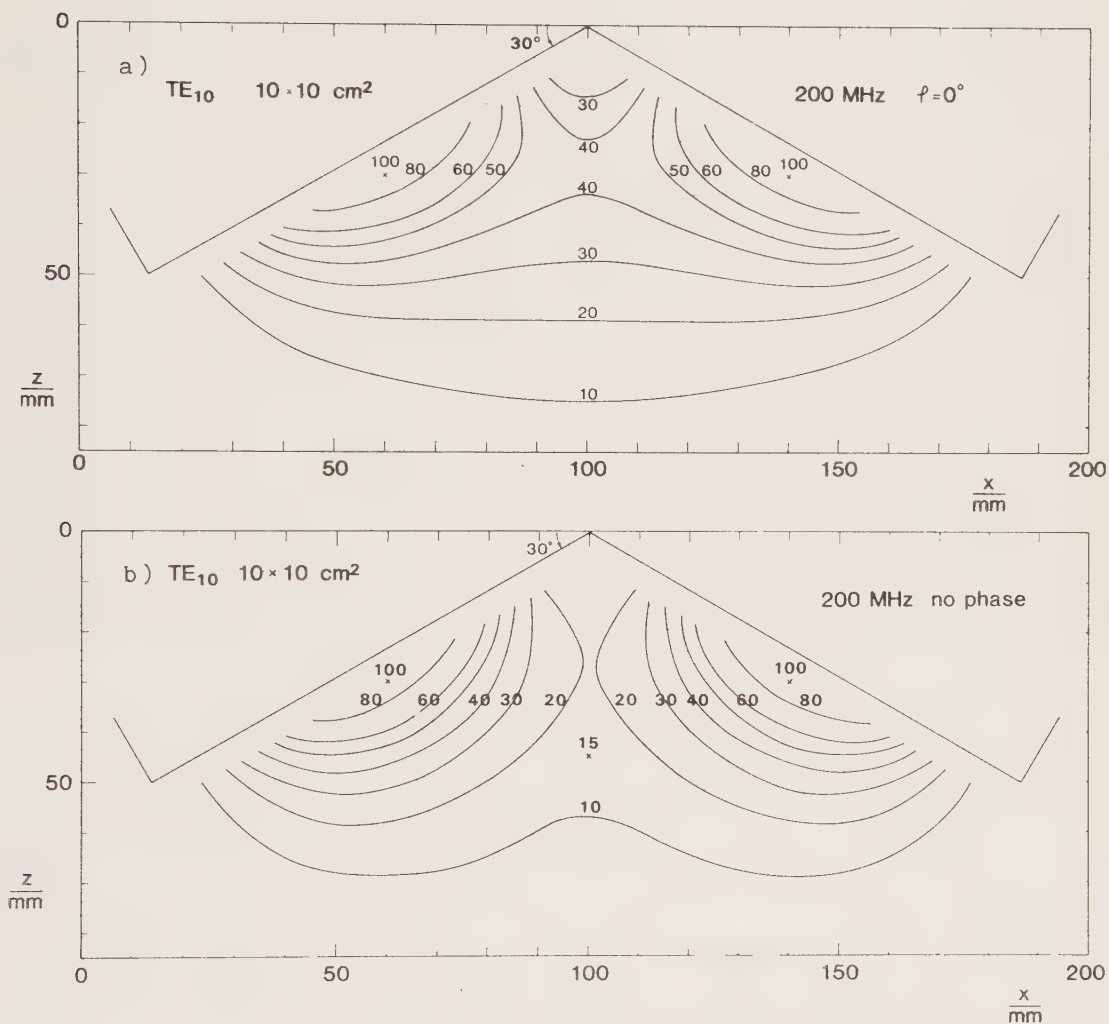


Fig. 14. Iso-absorbed-power distribution from two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators tilted 30° at 200 MHz with
a) coherent fields in phase
b) non-coherent fields.

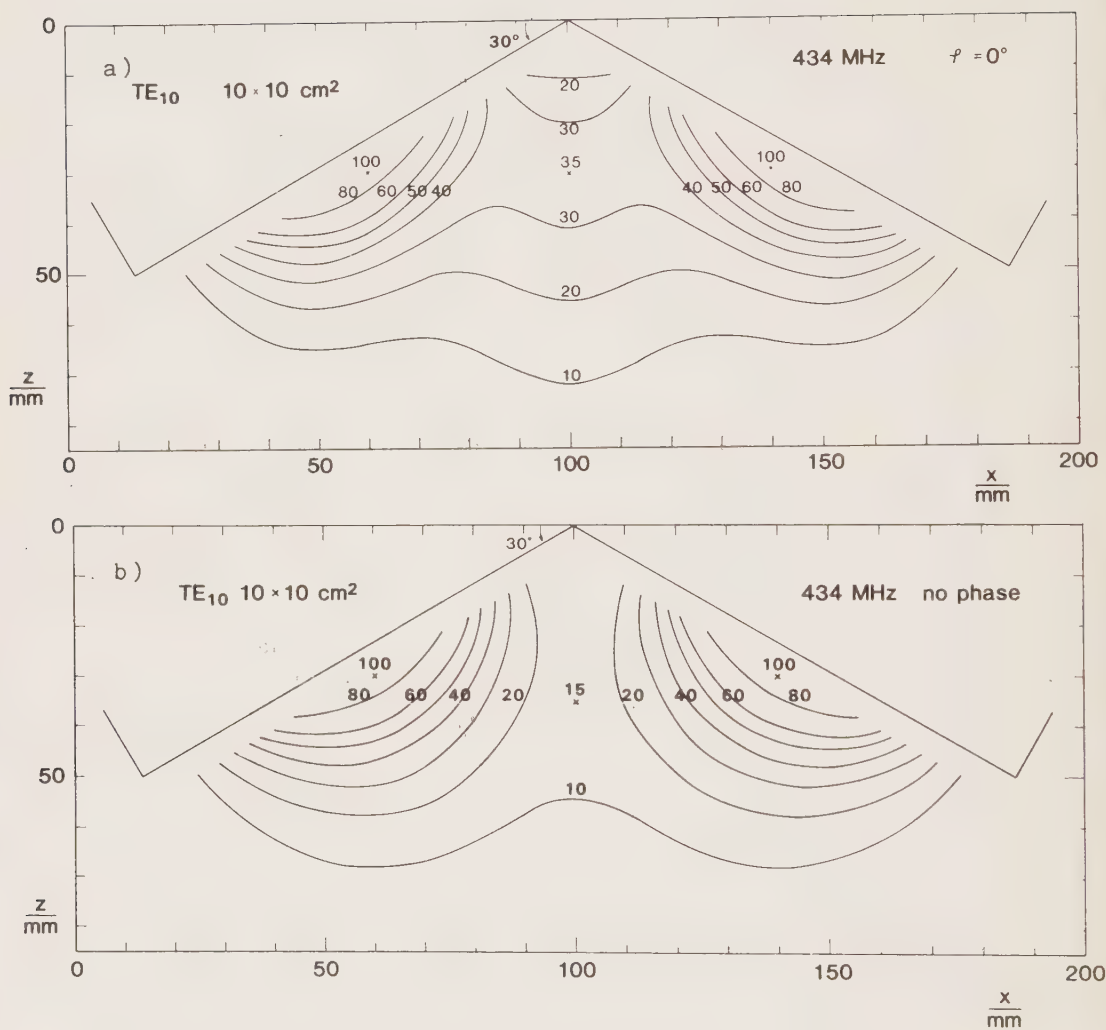


Fig. 15. Iso-absorbed-power distribution from two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators tilted 30° at 434 MHz with
a) coherent fields in phase
b) non-coherent fields.

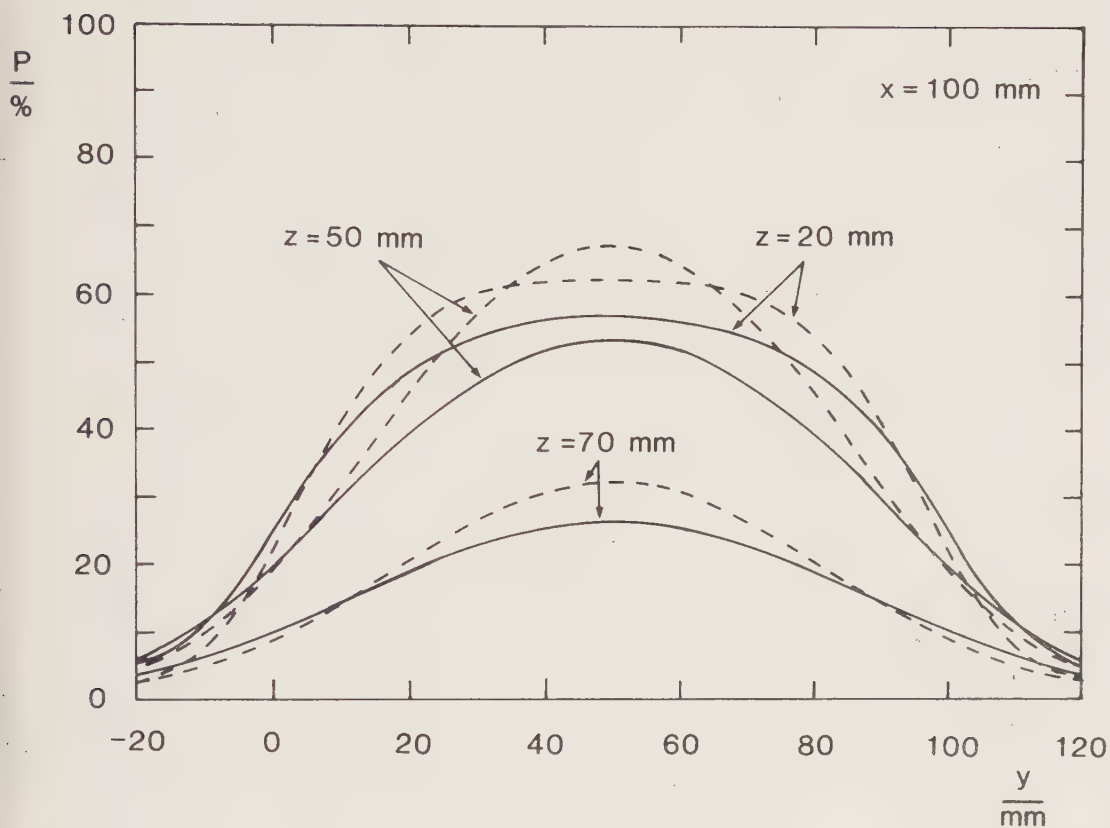


Fig. 16. Absorbed power distribution parallel to the incident electric field from two $10 \times 10 \text{ cm}^2$ TE_{10} -applicators tilted 45° and excited in phase at 200 MHz (—) and at 434 MHz (---).

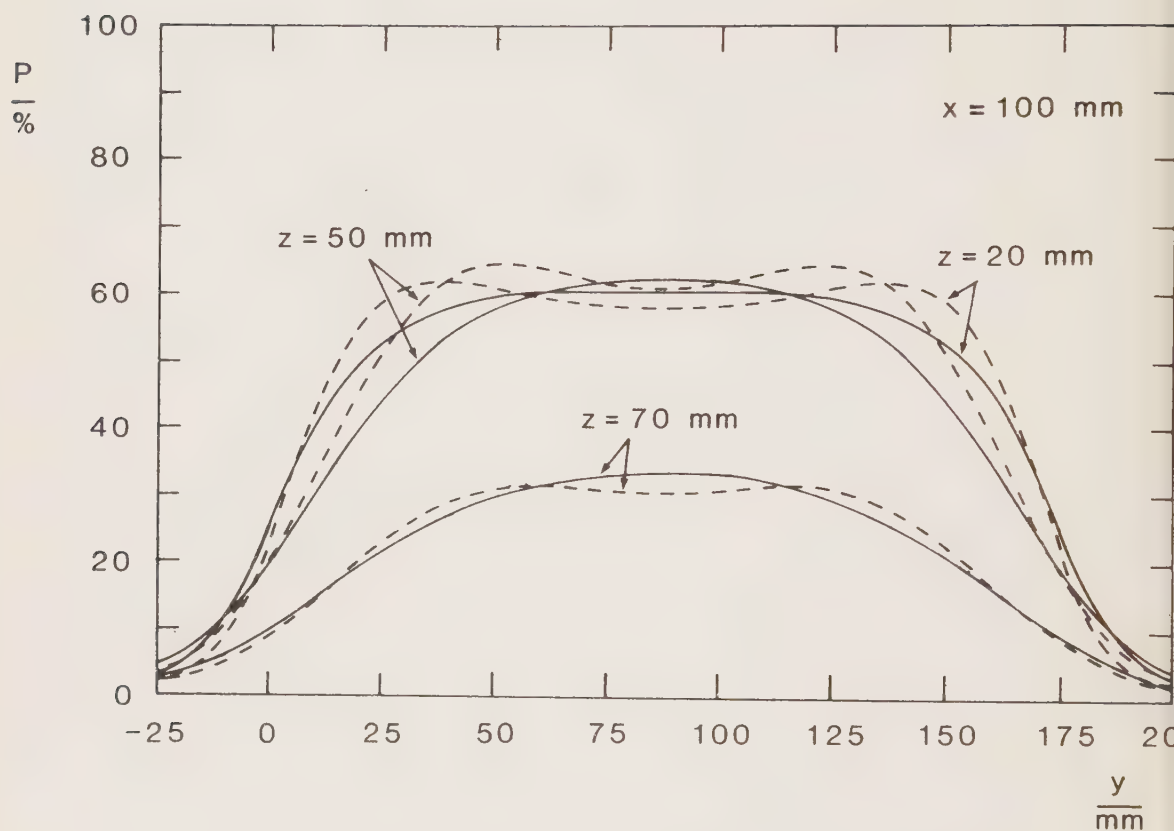


Fig. 17. Absorbed power distribution parallel to the incident electric field from two $10 \times 17.5 \text{ cm}^2$ TE_{10} -applicators tilted 45° and excited in phase at 200 MHz (—) and at 434 MHz (---).

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MICROWAVE-INDUCED HYPERTHERMIA AND IONIZING RADIATION

Preliminary clinical results

C.-E. LINDHOLM, E. KJELLÉN, T. LANDBERG, P. NILSSON and B. PERSSON

Observations on the effect of hyperthermia on malignant tumours date back before the detection of roentgen rays. Thus BUSCH (1866) reported on the regression of a sarcoma in a patient during a febrile episode. Probably on the basis of such observations COLEY developed a toxin to produce fever, and reported in 1893 some good results when treating tumour patients with the toxin.

WESTERMARK (1898) used local hyperthermic in advanced gynaecologic tumours, and noted some remarkable results. The local heating was achieved by means of a hot water coil that was applied to the tumour surface.

The clinical use of hyperthermia in combination with ionizing radiation was described in 1909 by DE KEATING-HART and by SCHMIDT.

Only few reports on hyperthermia in tumour treatment appeared in the next six decades, a possible explanation being that the methods to induce general as well as local hyperthermia were insufficient. Furthermore, other treatment modalities such as effective radiation therapy became available. In recent years the interest in local hyperthermia in tumour treatment has rapidly grown, and different heating methods are being used, among them microwave technology, to produce controlled heating (SANDHU et coll. 1978, JOHNSON et coll. 1979, U et coll. 1980, ARCANGELI et coll. 1980, NILSSON et coll. 1982).

The effect of heat on normal as well as malignant cells has been extensively investigated, mainly in

vitro but also in vivo. Reviews on the subject were given by SUIT & SHWAYDER (1974), GERNER et coll. (1975), DEWEY et coll. (1977), OVERGAARD & OVERGAARD (1977), OVERGAARD (1977, 1979) and FIELD & BLEEHEN (1979). A difference in the response to heating seems to exist at approximately 43°C. At higher temperatures, irreversible changes occur in both normal and malignant cells (DEWEY et coll. 1971, 1977, HARISIADIS et coll. 1975, LEITH et coll. 1977), especially in the nucleus, whereas at temperatures in the range of 41° to 43°C changes are more readily reversible. In the lower temperature range in vitro and in vivo series indicate, that malignant cells may also be intrinsically more heat sensitive than normal cells, which makes this temperature range especially attractive. Some contradictions exist, however, to the statement of an inherent, selective sensitivity of malignant cells to heat.

Clinical experience today indicates that hyperthermia alone will produce complete response only rarely, whereas the combination of hyperthermia and ionizing radiation has been reported to give complete response frequently (OVERGAARD 1982). Therefore, much of the research today explores combinations of hyperthermia and other treatment modalities, and then in particular ionizing radiation.

In fractionated hyperthermia treatment so called thermal tolerance will have to be taken into consideration (SELAWRY et coll. 1957, GERNER et coll.

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Table 1

Details about the patient series. Group A: Only one lesion. Group B: Multiple lesions

Group	Case No.	Sex	Age (years) at hyperthermia	Year of diagnosis and years of recurrence	Previous therapy (year)	Actual tumour localization at hyperthermia	No. of sites treated (XRT and HT)
B	1	F	57	Adenoca. of the right breast 1961 Locally recurrent 1963, 1965, 1973, 1974 Locally progressing recurrences from 1977-80	Surgery and postop. XRT 44.0 Gy to the axillary region 1961-74, 56.0 Gy to the chest wall 1965-75 Androgens + oophorectomy + corticosteroids 1966 Antioestrogens 1975 Prednimustine 1979	Locally in previously operated and irradiated ventral chest wall and right axilla	4
A	2	F	48	Adenoca. of the right breast 1971 Malignant pleural effusion 1976 Metastases to the right axilla 1978	Surgery and postop. XRT, 28.0 Gy, 1971, chest wall and axilla CTX + ADR + FU 1976 Oophorectomy 1977 MTX + ALK 1978 CTX + FU + antioestrogen 1979	Sub- and intracutaneous metastases to the right axilla, being irradiated before	1
B	3	M	69	Undiff. ca. of the left parotid gland, with regional and pulmonary metastases Aug. 1980	Local excision and four courses of VCR + ADR + CTX + VP-16 1980	Primary tumour and regional metastases, being unresponsive to chemotherapy	2
B	4	F	69	Papillary adenoca. of right axilla and breast (breast ca. ?) 1978 Multiple cutaneous metastases 1980	Surgery and postop. XRT, 60.0 Gy, 1978 VCR + ADR + CTX + MTX 1978-79, FU + MM 1979 Antioestrogen 1978-79 Oestrogen + gestagen 1979 Interferon 1979-80, ADR + VIND weekly and Prednimustine 1980	Cutaneous ulcerating metastases on the anterior and posterior chest wall, 2 of 5 being irradiated before	5
A	5	M	71	Dissem. uroepithelial ca. of the bladder April 1980	XRT to metastases in the right eye June 1980	Subcutaneous metast. in the right anterior chest wall	1
A	6	F	51	Adenoca. of the right breast 1978 Locally recurrent March 1980 Locally recurrent Sept. 1980	Preop. XRT 30.0 Gy combined with CTX + BLM + FU 1978 Antioestrogen May 1980 Local excision March and Sept. 1980	Anterior chest wall after excision considered microscopically not radical. (No parameter to follow.) Previously irradiated	2
A	7	M	68	Epitheloid cell sarcoma of the right arm March 1980 Metast. to right axilla and bone Sept. 1980	Amputation of the right arm March 1980 XRT to the right hipbone, 30.0 Gy, Oct. - Nov. 1980	Metastases in the right axilla	1

XRT=Radiation therapy, HT=hyperthermia, CTX=cyclophosphamide, ADR=doxorubicin, MTX=methotrexate, ALK=melphalan, VCR=vincristine, BLM=bleomycin, FU=5-fluorouracil, MM=mitomycin, VIND=vindesine.

Table 2*Scoring of skin reaction (modified after WHO 1979)*

Grade 1	
a	No visible reaction
b	Minimal erythema
c	Marked erythema
Grade 2	
a	Erythema with desquamation
b	Dry desquamation
Grade 3	
a	Desquamation with blisters
b	Moist desquamation
Grade 4	
a	Small necroses or ulceration
b	Massive ulceration

1976, LAW & HUME 1980, NIELSEN & OVERGAARD 1979). Thermal tolerance implies that it may take up to 72 hours before the next heat session will yield the full effect after an earlier heat session.

In combined hyperthermia and radiation therapy the thermal enhancement of the ionizing radiation effects in surrounding normal tissues must also be considered, as well as the sequence of the two modalities. Some experimental implications exist for giving hyperthermia after radiation therapy instead of vice versa (FIELD *et coll.* 1977, MYERS & FIELD 1977, STEWART & DENEKAMP 1978, FIELD & BLEEHEN, OVERGAARD 1980). OVERGAARD concluded that a small number of weekly hyperthermia fractions gives a better therapeutic gain factor in combined treatment than daily hyperthermia fractions.

Both systemic and local hyperthermia have been used. Local hyperthermia has been induced by radiofrequency techniques, microwaves or ultrasound. The thermometry has presented a problem, and then in particular for microwaves and radiofrequency heating. Usually temperature recordings during a hyperthermia session by means of invasive techniques are reported (JOHNSON *et coll.*, KIM & HAHN 1979, MARMOR *et coll.* 1979, ARCANGELI *et coll.*, BICHER *et coll.* 1980, U *et coll.*). The temperature rise in the series has varied. The length of each hyperthermia session as well as the total number of sessions and their interval has also varied (20–120 min). No principles for this new treatment modality are today firmly established, neither when used alone nor in combination with ionizing radiation.

In order to make relevant observations on tissue

response to hyperthermia, a good control of the heating is needed. A computer control system for local microwave induction of hyperthermia in superficial tumours has been developed (NILSSON *et coll.*). The purpose of the present communication is to report on the preliminary clinical results using this system to control the hyperthermia given according to a prescribed treatment protocol. This has been constructed to compare the effect of different treatment schedules, considering the experimental as well as early clinical experiences.

Material and Methods

From August 1980 to January 1981 a total of 7 patients with microscopically confirmed superficial malignant tumours were treated (Table 1). The follow-up ended on 1 November 1981. All tumours were considered to be refractory to other therapy.

Of 16 tumour sites in the 7 patients, 9 had previously been treated by irradiation and chemotherapy and 5 by chemotherapy alone. Two sites had not been treated earlier. Four patients (group A) had one lesion only and 3 (group B) had multiple lesions, which were treated with different modalities.

Hyperthermia was induced by means of 2450 MHz microwaves (NILSSON *et coll.*). The microwave applicator allowed for heating of tumours of at most 7 cm surface diameter and a depth of at most 3 cm from the skin surface, evaluated by palpation. Only patients with this size of the tumours or less were included in the series. Thermistor probes (YSI Inc., USA, model 511) with a diameter of 0.6 mm were introduced into the tumour at 2 or 3 different positions, and 1 or 2 thermistors were placed on the skin. One of the thermistors was chosen as master and the aim was to maintain a temperature at the master probe of 42.5°C during 45 min via the computer control system. The temperature values recorded by each thermistor were stored by the computer. The temperature and time were chosen according to values found in the literature and estimated as reasonable with respect to the patients well-being.

The tumours were calipered if possible, and the tumour response was recorded according to WHO recommendations (1979). Skin reactions were graded according to an 8-point scale (Table 2), modified after WHO. Fine needle aspiration biopsy was used in 2 patients (Nos 1 and 3) for cytologic examination.

Different treatment schedules were used (Table 3) to enable a comparison between ionizing radiation alone, hyperthermia alone and hyperthermia combined with irradiation. For this purpose it was assumed that all different tumours in a particular patient were biologically identical with respect to response to the different treatment modalities.

Three different combinations of hyperthermia and ionizing radiation were chosen with the aim to evaluate the effect of different time intervals between irradiation and hyperthermia, and also to record the effect of different numbers of hyperthermia sessions (Table 3). The basic schedule III (Table 3) includes 2 hyperthermia sessions weekly for 2 weeks. One reason for only 2 hyperthermia sessions a week was to take thermal tolerance into consideration. Another reason was that daily irradiation and hyperthermia, used simultaneously or sequentially, give thermal enhancement of the ionizing radiation effect in the surrounding normal tissues, resulting in no or very low therapeutic gain factors (OVERGAARD 1980). Schedule II was designed to elucidate whether only one hyperthermia session per week was sufficient. Schedule IV was designed to compare the therapeutic ratios of hyperthermia and ionizing radiation given simultaneously versus spaced by 4 hours (schedule III). For practical reasons hyperthermia was started 30 to 60 min after ionizing radiation was given in 'simultaneous' treatment.

The radiation absorbed dose chosen (30 Gy in 10 fractions over 12 days, the corresponding CRE-value being 13.1) often is a useful target absorbed dose



Fig. 1. Hyperthermia treatment set up.

in repeated irradiation of a local recurrence (e.g. of carcinoma of the breast).

Only one patient in the series had a sufficient number of lesions to allow for all schedules. For the other patients treatment modalities were used which on the basis of literature reports (STEWART & DENEKAMP, OVERGAARD 1978) were considered to give the best result. Thus, patients with only one lesion for hyperthermia were treated according to schedule III (Table 3).

Skin cooling with circulating air was used in 2 patients (Nos 3 and 4, Tables 1, 3).

A typical treatment set up is illustrated in Fig. 1.

Results

The preset temperature at the master thermistor could almost always be maintained at $\pm 0.5^\circ\text{C}$ at a

Table 3

Fractionation schedules for radiation therapy and hyperthermia alone or in combination. Normal treatment is given over 2 weeks. The irradiation was given by means of conventional roentgen rays, ^{137}Cs gamma rays or electrons. Dose specified according to ICRU Report No. 29 (1978)

Schedule	Day 1	Day 2	Day 3	Day 4	Day 5
I	XRT	XRT	XRT	XRT	XRT
II	XRT	XRT	XRT	XRT	XRT+HT,
III	XRT	XRT+HT _i	XRT	XRT	XRT+HT,
IV	XRT	XRT+HT _s	XRT	XRT	XRT+HT,
V	HT				
VI	No treatment				

XRT=Radiation therapy (3 Gy target dose per fraction).

HT=Hyperthermia (42.5°C for 45 min.).

HT_i=Four hours interval between irradiation and hyperthermia.

HT_s=Irradiation and hyperthermia 'simultaneously' (hyperthermia started within one hour after irradiation).

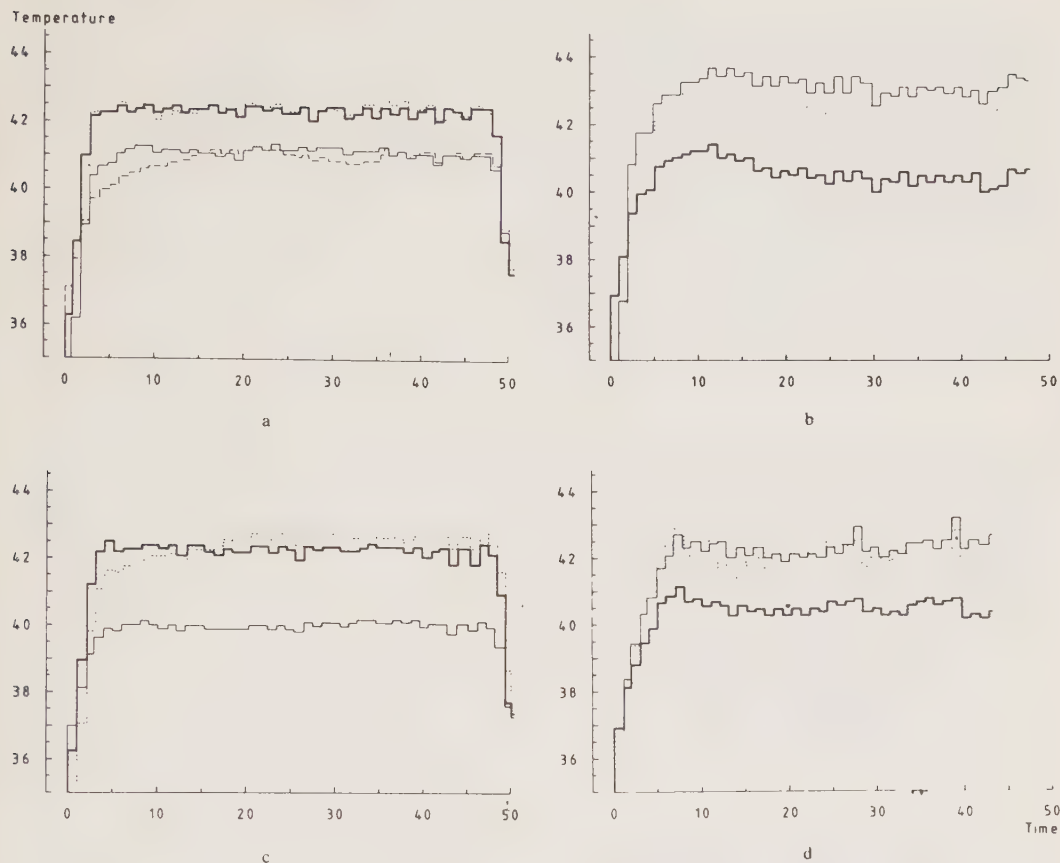


Fig. 2. Temperature profiles at 4 different hyperthermia sessions in patient No. 3. The thick curves indicate the master probe temperature. The histograms show the mean temperature ($^{\circ}\text{C}$) for each minute. a) Centrally at 7 mm depth in tumour (—). Centrally on the skin (—). Centrally at 20 mm depth in tumour (---). b) The master probe temperature had to be decreased due to high temperature readings at the other probes. Centrally at 10

mm depth in tumour (—). Centrally on the skin (—). Peripherally on the skin (---). c) Centrally at 7 mm depth in tumour (—). Centrally at 20 mm depth in tumour (—). Centrally on the skin (---). d) The master probe temperature had to be decreased due to high temperature readings at the other probes. Centrally at 7 mm depth in tumour (—). Centrally at 20 mm depth in tumour (—). Centrally on the skin (---). Time in minutes.

session, and the heating system thus proved to be reliable.

On the other hand, differences in temperature between the different thermistors at a session was common (0.3°C at the least and 3.5°C at the most, Figs 2-4). This may be explained in different ways: (1) Inadequate homogeneity in the primary microwave beam, (2) inadequate coupling between the microwave applicator and the surface of the patient, (3) variations in microwave absorption in different tissues that are relevant for the heat distribution, and (4) variations in blood circulation in the heated volume. If the temperature at other thermistors than

the master tended to increase to higher values (e.g. 43.9°C and 43.0°C , respectively, on the skin, Fig. 2b, d) the preset temperature value for the master thermistor was decreased during the treatment.

It was the intention to place the thermistor in the same position at each hyperthermia treatment. For this purpose a detailed drawing was made at the first session. Usually the temperature readings agreed well at the different sessions, but in some instances (Fig. 2) variations occurred.

Apparently circulatory conditions were of importance. Thus, in tissues that were clinically fibrotic after previous irradiation it was relatively easy to

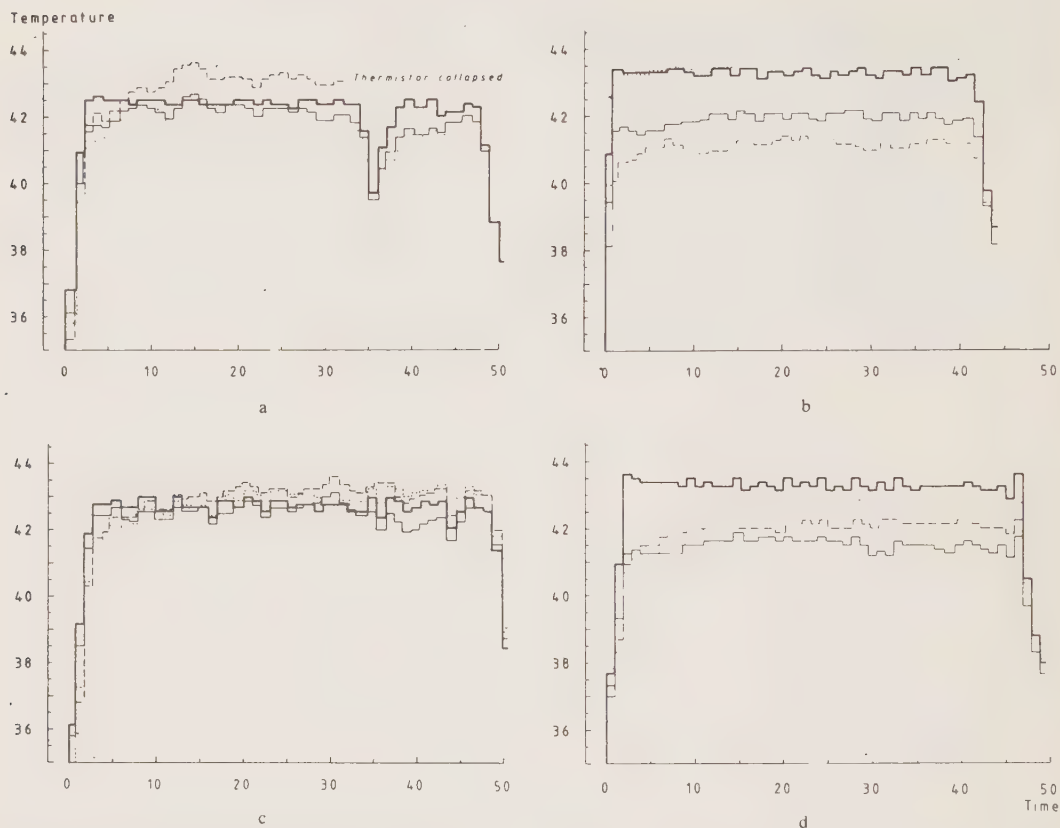


Fig. 3. Temperature profiles at 4 different hyperthermia sessions in patient No. 4. The thick curves indicate the master probe temperature ($^{\circ}\text{C}$). Centrally at 3 mm depth in tumour (—). Peripherally at 3 mm depth in tumour (—). Centrally on the skin (---). Time in minutes.

Peripherally at 3 mm depth in tumour (—). Centrally on the skin (—). Peripherally on the skin (---). Time in minutes.

maintain a steady and apparently homogeneous temperature. Temperature profiles for such a patient, who had previously received 60 Gy to the heated volume, is shown for all 4 hyperthermia sessions in Fig. 3. Especially during 2 of the sessions (Fig. 3a, c) a relatively small temperature difference occurred between the thermistors but during the other 2 sessions (Fig. 3b, d) larger temperature differences were noted. Furthermore, in relatively large tumours (Fig. 4, the size of this tumour being 3.9 cm $\times$ 4.1 cm) the central temperature could be maintained at a high temperature even at a relatively large depth without causing overheating to overlying tissues.

Fig. 5 shows the tumour response in 2 sites in patient No. 1 (Tables 1, 4) during and after combined hyperthermia and radiation therapy. In this

patient 6 tumours measuring 5 to 8 mm were treated only by ionizing radiation. They did not decrease in size during the treatment period and 3 weeks after. They were then excised and microscopic examination showed remaining tumour.

The variations in size of 4 different tumours in a patient with disseminated carcinoma of the left parotid gland (patient No. 3, Tables 1, 4) appear in Fig. 6. Combined hyperthermia and radiation therapy was given to the tumour in the parotid gland (schedule III, Table 3) whereas a metastatic node in the submandibular region was treated with ionizing radiation only. The lung metastases were not treated. The tumour given the combined treatment showed a partial remission, whereas the tumour only irradiated did not change in size, and the lung metastases progressed. At fine needle aspiration biopsy 3 times

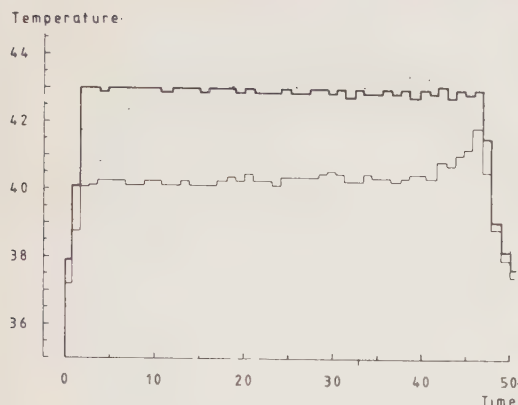


Fig. 4. Temperature profile in patient No. 5 at a hyperthermia session. The thick curve indicates the master probe temperature ($^{\circ}\text{C}$). The lower temperature at 4 mm depth compared with that at 20 mm depth can be explained by a lower absorption of microwaves in subcutaneous fat tissue. Centrally at 20 mm depth in tumour (—). Centrally at 4 mm depth in fat tissue (—). Centrally on the skin (---).

2 to 5 months after beginning of the treatment no malignant cells were found in the lesion given the combined treatment but remaining tumour cells were seen in the lesion treated with ionizing radiation alone. Later, slight progression of all the tumours indicated that vital tumour cells were left also in the tumour given the combined treatment. This patient, as well as patients Nos 2 and 4 (Tables I, 4), has during the follow-up period received local radiation therapy with or without new cytotoxic regimens due to progressive disease in other sites.

In 2 patients the treatment had to be discontinued due to deteriorating general condition (Nos 5 and 7), and one patient (No. 6) had no measurable disease. Therefore, the effect of the treatment on the tumours was only evaluable in 4 patients (Table 4). Of 8 tumours given a combination of hyperthermia and radiation therapy 5 showed a complete and 3 a partial response. The duration of the complete responses has ranged from 8 to 14+ months. One of 3 tumours given only radiation therapy showed objective response whereas 2 had a stable disease. The responding lesion only received 18 Gy due to previous extensive irradiation of this site. One lesion treated only by hyperthermia showed objective response. Thus, the rate of complete or partial response for the evaluable tumours in the present series was 8/8 for combined hyperthermia and radiation therapy but 0/3 for ionizing radiation alone and 0/1 for hyperthermia alone (Table 5). The combina-

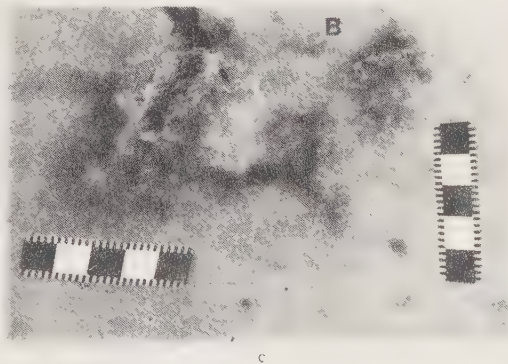
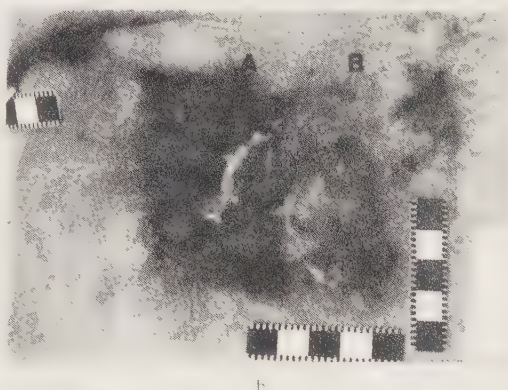
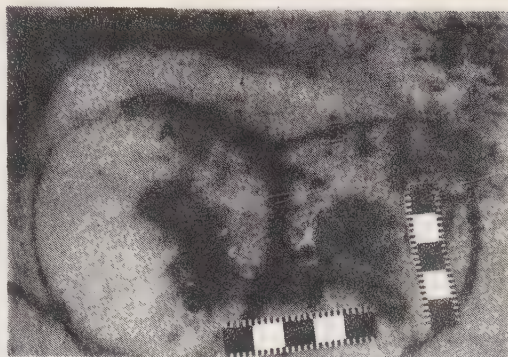


Fig. 5. Local recurrences of mammary carcinoma 19 years after surgery and radiation therapy, progressing during treatment with antioestrogens and cytostatics. Patient No. 1. a) Before combined irradiation and hyperthermia. Lesion A treated according to schedule IV and lesion B according to schedule III. b) Four weeks after conclusion of combined irradiation and hyperthermia. Lesion A totally necrotic (complete response), whereas lesion B is scored as a partial response. c) Twenty-two weeks after conclusion of combined irradiation and hyperthermia. Epithelialized tumour bed with small crusts. Fine needle aspiration biopsy at this occasion showed no malignant cells. Twelve weeks later the tumour recurred again in both sites.

Table 4

Evaluation of different schedules (cf. Table 3), modified after WHO (1979)

Case No. and diagnosis	Schedule						Initial tumour response	Follow-up (months after beginning of treatment)	Later recurrence or progressive disease (months after beginning of treatment)
	I	II	III	IV	V	VI			
No. 1. Mammary ca.	x						SD	0.5 (excision)	6
Recurrence in thoracic region		x					PR	10.0	8
			x				CR	10.0	8
				x			CR	10.0	8
							CR	14.0	No
No. 2. Mammary ca. with axillary and pulmonary met.			x						
No. 3. Anaplastic ca. in left parotid gland, met. in lymph nodes in neck and lungs	x		x				SD	11.0	2
						x	PR	11.0	5
							PD	11.0	Continuous
No. 4. Papillary ca. in axilla, breast and skin	x						OR	11.0	5
		x					CR	11.0	No
			x				PR	11.0	No
				x			CR	11.0	No
					x		OR	11.0	3
						x	PD	11.0	Continuous

CR = complete response, PR = partial response, OR = objective response (= decrease, but less than 50 per cent). SD = stable disease and PD = progressive disease.

Table 5

Microwave-induced hyperthermia and ionizing radiation. Summary of preliminary clinical results (November 1981)

	Complete response	Partial response	Objective response	Stable disease
Hyperthermia + radiation therapy	5/8	3/8	—	—
Radiation therapy alone	—	—	1/3	2/3
Hyperthermia alone	—	—	1/1	—
Duration (months)	8, 8, 11+, 11+, 14+	5, 8, 11+	3, 5	0.5, 2

tion of hyperthermia and ionizing radiation in the present series was thus superior to either method when used alone. However, the material is too small for a statistical analysis, and follow-up may be too short to warrant conclusions on the relative merits of the different treatment schedules or on any time-temperature response relationship.

Two side-effects of hyperthermia were observed in the present series. First, local pain, probably related to local overheating, occurred in 5 of the 7 patients, being at most of grade 2 ('moderate', WHO 1979) in 3 patients, and at most grade 3 ('severe') in 2 patients, all 5 requiring slight analgetic medication. The pain may persist for some hours

after heating. Secondly, skin burns were a problem (Table 6) and usually grade 3 or 4 skin reactions were noted after combined hyperthermia and ionizing radiation. No correlation could be found between previous radiation therapy and skin reaction. Up to now, healing of the skin burns has been uneventful. In 2 cases, however, it took 5 and 6 months, respectively, before the ulcers were completely epithelialised.

Discussion

The effect of hyperthermia on the cellular level has been extensively discussed. In the lower tempera-

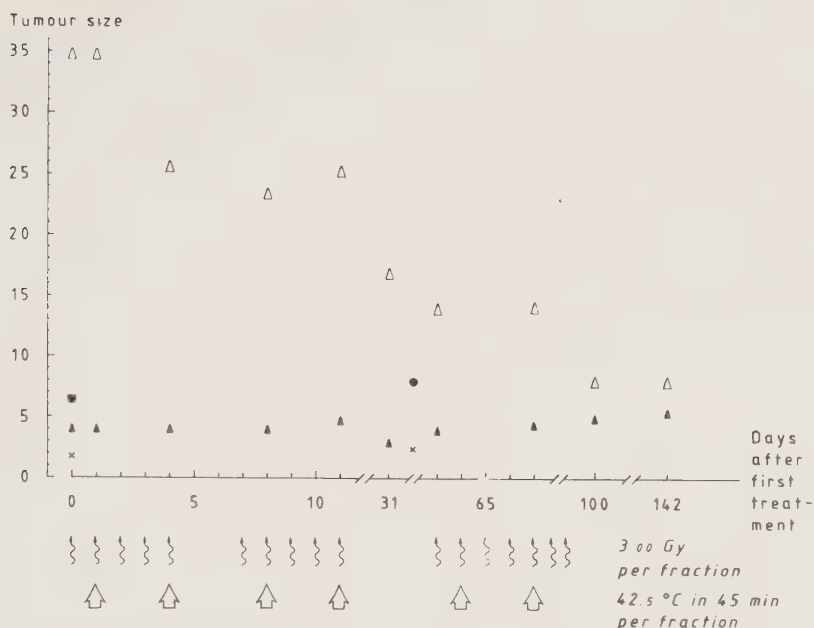


Fig. 6. Tumour sizes (cm²) at different follow-up intervals for a patient (No. 3) with anaplastic carcinoma in the left parotid gland, lymph nodes in the neck and in the lungs. The hyperther-

mia given 4 hours after irradiation. Radiation therapy + hyperthermia (Δ). Radiation therapy (▲). No treatment (●, x).

Table 6

Maximum skin reaction (graded according to Table 2)

Case No.	Schedule				
	I	II	III	IV	V
1	1b	4b	3b	4b	
2			4b		
3	1b		4a		
4	1b	1b	4a	3a	1c
6			3a		

ture range (41–43°C) several reports on in vitro and in vivo series indicate that malignant cells may be intrinsically more heat sensitive than normal cells, which makes this temperature range especially attractive (CAVALIERE et coll. 1967, CHEN & HEIDELBERGER 1969, LEVINE & ROBBINS 1970, MUCKLE & DICKSON 1971, OVERGAARD & OVERGAARD 1972, KASE & HAHN 1975, 1976, GIOVANELLA et coll. 1976, OVERGAARD 1976). Some authors, suggest that it is difficult to ascertain whether differential heat sensitivity in vitro in malignant cells versus normal cells is due to inherent cellular properties or to different culturing and medium conditions in various laboratories (HARISADIS et coll., BHUYAN 1979,

RAAPHORST et coll. 1979). The selective heat sensitivity of malignant tumours compared with normal tissue may be explained by differences in microenvironment due to different cell metabolism, e.g. partly chronic hypoxia, accumulation of lactic acid, and reduction of pH in tumours (OVERGAARD & OVERGAARD 1972, OVERGAARD 1977, GERWECK et coll. 1979). The observed heat sensitivity in tumours may also be explained by selectively higher temperature, caused by inefficient blood flow in tumours, resulting in poorer cooling than in normal tissue (LE VEEN et coll. 1977). Abnormalities in the microvasculature of tumours subjected to hyperthermia, resulting in microvascular occlusion (stasis, thrombosis) and ending in more or less obstruction of the tumour circulation may be an important part of the selective sensitivity of malignant tumours to hyperthermia (EDDY 1980, EMAMI et coll. 1981).

Cell necrosis and pyknosis may occur rapidly after hyperthermia. A few hours after hyperthermia an increased lysosomal activity occurs and lysosomal enzymes, such as acid phosphatase, are released. The ultrastructure of experimental, solid malignant tumours, exposed to hyperthermia in vivo, is characterized by rapid cytoplasmic swell-

ing, rupture and segmentation of the plasma membrane, dilatation and rupture of mitochondria and condensation of heterochromatin near the nuclear envelope, and around nucleoli (OVERGAARD 1976, FAJARDO *et coll.* 1980). The nuclear envelope seems most resistant to hyperthermia but finally marked separation of the two layers of the nuclear membrane occurs.

The lysosomal activity after hyperthermia treatment is most marked at low pH (OVERGAARD 1976), which *per se* seems to enhance the thermal cell inactivation both in malignant and normal cells (BICHEL & OVERGAARD 1977, GERWECK & RICHARDS 1981). Low pH is a common feature of neoplastic tissue with its tendency to elevated rate of lactic acid production, even under oxygenated conditions (NAESLUND & SWENSON 1952, EDEN *et coll.* 1955, GULLINO *et coll.* 1964, GERWECK *et coll.*). Hypoxia further increases the rate of lactate production (DALES 1960, GERWECK *et coll.*). Compared with the effect of heating of oxygenated tissue, however, increased cell killing by hyperthermia may occur under chronic hypoxic conditions, even if pH is normal or acute reoxygenation is given before treatment (GERWECK *et coll.*). Thus, chronically hypoxic cells are more susceptible to hyperthermia than well oxygenated cells.

Hyperthermia decreases the synthesis of RNA and DNA (MONDOVI *et coll.* 1969, GIOVANELLA *et coll.* 1970, HEINE *et coll.* 1971, DICKSON & SUZANGAR 1974). Most observations are made under *in vitro* conditions but there are also morphologic observations demonstrating a similar effect in solid tumours *in vivo* (OVERGAARD 1976). The effect on RNA is postulated to be primary to that on DNA and consists of inhibition of both synthesis and conversion of precursor RNA to mature RNA. Being reversible and non-selective for malignant cells, this effect may be of little clinical importance (OVERGAARD 1977).

Cells in S-phase and non-cycling plateau-phase cells seem to be more sensitive to hyperthermia than cells in other phases of the cycle (WESTRA & DEWEY 1971, HAHN 1974, BHUYAN *et coll.* 1977). This offers another promising rationale for the combination of hyperthermia and ionizing radiation, since the two methods have their main effects on different phases of the cell cycle. Apart from these differences in cytotoxic effect hyperthermia also seems to be sensitizing to radiation by means of a decreased repair of RNA and DNA (BEN-HUR *et coll.* 1974).

Since ionizing radiation and hyperthermia differ in their effect mechanism first on hypoxic cells and secondly on different phases of the cell cycle, and since hyperthermia seems to decrease the cell repair of ionizing radiation changes to the cells, the combination of the two treatment modalities is attractive. Hyperthermia may then also be an alternative or additive method to, e.g. hypoxic cell sensitizers or high LET radiation to increase the ionizing radiation effect on hypoxic tumour cells. A special clinical indication is previously irradiated tumours, since a relatively small radiation absorbed dose may still be useful when given in combination with hyperthermia.

The effects of hyperthermia are closely related to the temperature and also to the heating time (MORRIS *et coll.* 1977, OVERGAARD 1979, OVERGAARD & SUIT 1979). The repair of sublethal heat injury is considered to take place within 4 to 6 hours (ALFIERI *et coll.* 1975), and then slower for tumour cells than for their normal counterparts. In the combined treatment with hyperthermia and ionizing radiation, the most evident effects occurred when they were given simultaneously, whereas sequential treatment with an interval of at most 4 to 6 hours gave the largest therapeutic gain, even though the total effect then was the least (MYERS & FIELD, STEWART & DENEKAMP, OVERGAARD 1979). It is not clear whether heat should be applied before or after ionizing radiation in sequential treatment.

The clinical combination of hyperthermia and ionizing radiation has been the subject of several reports, dealing mainly with unrandomized series.

HORNBACK *et coll.* (1977) reported 70 patients, treated with a combination of microwave hyperthermia and ionizing radiation. Of 20 patients, eligible for a minimum of 9 months follow-up, complete regression of the tumours was noted in 80 per cent. All patients had malignant tumours that were previously refractory to further treatment.

KIM *et coll.* (1977) treated 36 patients with either hyperthermia or ionizing radiation alone or combined. Most patients had cutaneous lymphomas. Complete and partial response, usually transitory, could be seen after hyperthermia alone. Seven of 10 patients with locally recurrent tumours had a significantly prolonged benefit after combined treatment. The initial tumour regression was faster in patients treated with both modalities than with ionizing radiation alone. The effect of the combined treatment on

the normal tissues did not appear to be greater than after radiation therapy alone.

BICHER *et coll.* (1980) used a combination of hyperthermia and ionizing radiation to treat 37 lesions in 23 patients. Melanomas and lymphomas responded best, sarcomas were the most resistant tumours, and adenocarcinomas and squamous cell carcinomas were in between.

A number of recent clinical reports on the effect on different tumours by hyperthermia alone as well as irradiation versus combined heat and irradiation has been listed by OVERGAARD (1982). The pooled results in 276 patients in 12 reports showed that when hyperthermia alone was used the complete response rate was 13 per cent, whereas partial response occurred in 39 and no response in 48 per cent.

In 6 other series radiation therapy alone was compared with hyperthermia combined with radiation therapy, the total number of patients being 186. Radiation therapy alone resulted in complete response in 31 per cent compared with 74 per cent for the combined treatment modality.

The present preliminary series shows that combined microwave-induced hyperthermia and ionizing radiation was highly effective to induce complete response. It could be used successfully in previously irradiated patients.

When analysing the results (Table 4) of the different treatment schedules (Table 3) it appears that the small material does not warrant conclusions regarding any differences between the different combinations of hyperthermia and ionizing radiation.

Side effects, which included pain upon heating and skin burns, were tolerable. These side effects may largely be due to uneven thermal distribution, and they could be diminished with proper coupling of the microwave applicator and the patient. A homogeneous temperature elevation in the heated volume will be difficult to obtain due to the influence of factors such as the blood flow and different microwave absorption in various tissues. In the present series it was possible to maintain a precise temperature at the master probe. Measurements of the temperature at other sites confirmed the presence of uneven thermal distribution. This may present a problem, since deviation in temperature, already by less than 1°C, may be biologically significant, judging from experimental reports (MORRIS *et coll.*, OVERGAARD 1979, OVERGAARD & SUIT). However, in clinical situations higher temperatures (above

43°C) may be found in the tumour along with lower temperatures (below 43°C) in the normal surrounding tissue. This may give an individual enhancement of the therapeutic gain and ought not to be unfavourable as long as normal tissue is not injured. The reversed situation, on the other hand, will present a problem and may reduce or exclude the possibility of a therapeutic gain, at least if normal tissue will not repair hyperthermia damage more rapidly than the tumour. An actual problem in the present series was the tendency to heat accumulation of the skin during continued treatment time (Figs 2c, 3a, b, c, 4). A good cooling system seems to be necessary.

Obviously hyperthermia is a promising new treatment modality for malignant tumours, being well worth to be further explored. The most important difficulty in clinical situations seems to be to achieve a suitable thermal distribution. There is obviously a need for development in the field of heating technology and for creating standardized conditions for prospective trials. The development of a non-invasive temperature reading system is also desirable.

Hyperthermia has, until enough experience has been accumulated, mainly been used in patients with relatively superficial tumours, considered refractory to other treatment. Repeated treatment of previously irradiated volumes with combined hyperthermia and ionizing radiation is a particularly promising indication. The optimum combination of hyperthermia and ionizing radiation will have to be further explored. It may well be different for different tumours.

SUMMARY

The combination of microwave-induced (2450 MHz) hyperthermia and ionizing radiation was used in 7 patients with superficial malignant tumours, which were considered refractory to other therapy. A newly developed heating system was used, allowing for a maintained temperature at the master probe of $42.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ during 45 min, but temperature measurements at multiple sites showed a marked variation. This preliminary series indicates that the combination of hyperthermia and ionizing radiation may be useful, the response rate (complete or partial) being 8 of 8 evaluable lesions. Even previously heavily irradiated sites responded. Technical improvements are highly needed to allow for controlled heating of any tissue volume.

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